PROSPECTIVE IDENTIFICATION OF CLINICALLY RELEVANT RISK FACTORS INFLUENCING ILLNESS COURSE IN CHILDHOOD- AND ADOLESCENT-ONSET PSYCHOTIC DISORDERS

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ABSTRACT

ABIGAIL M. JUDGE: Prospective identification of clinically relevant factors influencing illness course in childhood- and adolescent-onset psychotic disorders.
(Under the direction of David Penn, Ph.D.)

Background: Psychotic disorders with an onset in childhood and adolescence are associated with a more severe illness presentation and malignant course than those with an onset in adulthood. Despite this, their longitudinal course has been studied only to a limited extent. Accordingly, the current study prospectively evaluated the predictive effects of clinically relevant factors on illness course. Methods: Hierarchical linear modeling and multiple regressions were utilized to evaluate the predictive effects of risk factors on level of psychiatric symptoms at 2-5 year follow-up among children and adolescents with well characterized psychotic disorders. Results: Psychotic and general symptoms decreased significantly over time but none of the examined covariates explained significant variance in the observed changes. Supplementary analyses evaluated the effects of two design characteristics (i.e., study effect and rater bias) on the observed changes and found significant rater effects with respect to measures of select psychotic symptoms. Discussion: General psychiatric symptoms decreased during the follow-up period with a significant interaction to characterize this change. Observed changes in psychotic symptoms appear to be artifacts of rater bias. Clinical and methodological implications are discussed.

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CHAPTER 1

INTRODUCTION

Prospective, longitudinal research on youth at-risk for developing schizophrenia helped contribute to the emergence of developmental psychopathology as an essential theoretical perspective (Cicchetti, 2006; Watt, Anthony, Wynne, & Rolf, 1984), one that emphasizes the origins and course of individual patterns of behavioral maladaptation across the lifespan (Sroufe & Rutter, 1984). Ever since, longitudinally-based developmental research on schizophrenia has helped describe its neurodevelopmental origin and the substantive heterogeneity of its etiology, neuropathology, and course (Walker, 1991). However, very few studies have applied principles of developmental psychopathology to research on risk factors that influence the course of psychotic illness in childhood and adolescents. A more refined understanding of such developmental phenomena may allow for application to sorely needed treatment research for this understudied child population.

The proposed study sought to evaluate risk factors associated with a more severe longitudinal course of psychotic illness among children and adolescents that may be relevant to future basic and treatment development research. With respect to psychotic disorder, there appear to be meaningful developmental variations in symptom presentation based on age of onset as well as important differences in illness course. However, previous research has suffered from methodological problems which affect interpretation.

Accordingly, I will begin with an overview of psychotic symptoms in childhood and adolescence with respect to illness prevalence, phenomenology, correlates, and longitudinal

course in order to emphasize the developmental variations in clinical presentation based on an earlier age of onset and to demonstrate the high need for services this young population may require. I will further provide an empirical and theoretical rationale for focusing on the current subset of youth with early onset psychosis, and describe the potential contributions of basic research on developmental risk factors to future treatment development for this population. Finally, I will conclude with a methodological critique of extant longitudinal studies in order to highlight the limitations of the available literature and the potential contributions of the current study.

Psychosis in childhood: prevalence, phenomenology, and course

Early onset psychotic disorders (EOP; i.e., onset of psychotic illness prior to age 18) are disabling conditions characterized by psychotic symptoms (e.g., hallucinations and delusions), impaired cognition, and social withdrawal (Asarnow, Tompson, & McGrath, 2004; McClellan et al., 2001; Semper & McClellan, 2003). Children and adolescents with EOP have more severe positive and negative symptoms, greater neurocognitive impairments, and higher rates of chronic functional impairment when compared to adults with the same illness (Ballageer, Malla, Manchanda, Takhar, & Haricharan, 2005; Hollis, 2000; Rapoport & Inoff-Germain, 2000; Yang, Liu, Chiang, & Chen, 1995).

Psychotic symptoms can be observed in the context of many childhood psychiatric disorders. These include schizophrenia spectrum disorders (Jacobsen & Rapoport, 1998), bipolar disorder (Carlson, Bromet, & Sievers, 2000; Varanka, Weller, Weller, & Fristad, 1988), major depressive disorder (Chambers, Puig-Antich, Tabrizi, & Davies, 1982; Ryan, Puig-Antich, Ambrosini, & Rabinovich, 1987) and disssociative disorders (Putnam, Hornstein, & Peterson, 1996). Hallucinations may also occur as part of reactive psychoses following stress and trauma (Hlastala & McClellan, 2005) and secondary to bereavement (Cepeda, 2007). However, the

diagnoses most frequently associated with psychosis in childhood and adolescents are mood disorders (Cepeda, 2007; Ulloa et al., 2000), and the diagnoses in which psychotic symptoms are most severe and chronic are schizophrenia spectrum disorders (McClellan, Werry, & Ham, 1993; Rapoport & Inoff-Germain, 2000).

Psychotic disorders affect approximately 1-5/10,000 children and as many as 1/200 adolescents (Burd & Kerbeshian, 1987; Tolbert, 1996; Volkmar, 1996), with the frequency of psychotic symptoms increasing with age (Carlson & Kashani, 1988; Volkmar, 1996). Clinical cohort studies report psychotic symptoms among 4-8% of clinically referred populations (Biederman, Petty, Faraone, & Seidman, 2004; Ulloa et al., 2000; Volkmar, 1996). Indeed, approximately 60% of individuals with schizophrenia develop symptoms for the first time during adolescence (Loranger, 1984).These data suggest that psychotic symptoms among clinically referred child populations, and adolescents in particular, are not as rare as commonly assumed.

The presence of psychotic symptoms in childhood is a major health hazard associated with marked functional impairment even outside of a defined schizophrenia spectrum illness. Such functional disability includes difficulties maintaining personal care and impairment in functioning within family and school contexts (Biederman et al., 2004; Castro-Fornieles, Parellada, Gonzalez-Pinto, & al, 2007). Higher rates of psychiatric comorbidity are observed among children and adolescents with psychotic symptoms when compared to other clinically referred youth (Biederman et al., 2004; Ulloa et al., 2000) as well as greater morbidity, including more frequent psychiatric hospitalizations (Biederman et al., 2004; Kumra, Jacobsen, Lenane, & al., 1998). Common comorbid syndromes include attentional problems, anxiety disorder and oppositional defiant disorder (Ross, Heinlein, & Tregellas, 2006; Ulloa et al., 2000).

The early onset of psychotic disorder commonly follows longstanding premorbid abnormalities such as chronic academic difficulties, social withdrawal, and behavioral problems (Castro-Fornieles et al., 2007; McClellan, Breiger, McCurry, & Hlastala, 2003; Schaeffer & Ross, 2002). Comparative studies of children and adolescents with psychosis in varying diagnostic contexts (i.e., schizophrenia, bipolar disorder, and psychotic disorder not otherwise specified) show significant levels of premorbid behavioral problems and academic difficulties across diagnostic groups, with youth with schizophrenia showing higher rates of social withdrawal and global impairment (McClellan et al., 2003). Indeed, youth with childhood-onset schizophrenia (i.e., onset prior to 12 years of age) show particularly severe premorbid histories which may reflect early neurodevelopmental manifestations of the disorder. Retrospective and cross-sectional studies of youth with childhood-onset schizophrenia demonstrate conspicuous premorbid developmental delays in speech and language, transient autistic symptoms, as well as longstanding and clinically significant attentional and learning problems (Alaghband-Rad et al., 1995; Asarnow, Brown, & Strandburg, 1995; Hollis, 1995; Jacobsen & Rapoport, 1998; Schaeffer & Ross, 2002). Thus, EOP emerges in the context of significant problems in normative development, and premorbid anomalies are especially severe among youth with schizophrenia spectrum disorders.

Youth with EOP demonstrate neurocognitive deficits more severe than those observed in individuals with an adult onset of the same illness (White, Ho, Ward, O'Leary, & Andreasen, 2006). Although neurocognitive impairments have been more extensively studied among adults with psychotic disorders, an expanding literature demonstrates similar impairments in children and adolescents with EOP. A recent critical review of this literature concluded that children with early-onset schizophrenia spectrum disorders show similar global deficits as those observed in adults (Wozniak, White, & Schulz, 2005). These deficits include intellectual impairments of

about 1.0 to 1.5 standard deviations below the mean for their age, problems with sustained attention, planning and flexibility, verbal and visual memory, fine motor performance, and visual spatial and visual organizational processing. Although neurocognitive impairments in childhood are not specific to EOP, the magnitude and breadth of observed deficits appears substantially wider among these youth than among other child populations (i.e., major depressive disorder, anxiety disorders, attention deficit disorder).

There is a more limited neuropsychological literature on youth with affective psychoses such as major depression and bipolar disorder. The few comparative studies of children and adolescents with affective psychoses and schizophrenia spectrum illness found no significant differences in overall neurocognitive profiles (Kumra et al., 2000; McClellan, Prezbindowski, Breiger, & McCurry, 2004), although youth with early onset schizophrenia spectrum disorders show greater global deficits and more severe deficits in social knowledge (McClellan et al., 2004).

Importantly, the functional significance of observed neurocognitive impairments in youth with psychotic disorders is not well defined. Among adults, neurocognitive deficits are more predictive of functional status than psychotic symptoms (Green, Kern, & Heaton, 2004) but this remains an understudied question among EOP. From a developmental perspective, however, the functional significance of neurocognitive deficits in adults is likely to be amplified when illness onset occurs at an earlier age and derails normative developmental processes. Thus, although the functional consequences of neurocognitive deficits in youth are not well characterized, their consequences on domains such as school and social functioning are likely quite severe and represent one contributor to the high level of psychosocial disability observed among this child population.

In addition to high rates of psychiatric comorbidity and marked neurocognitive impairments, psychotic symptoms and psychotic disorders in children and adolescents are

associated with suicidal ideation and attempts, especially among males (Jarbin & VonKnorring, 2004; Ulloa et al., 2000). Suicidality is more common among youth with early onset affective psychoses when compared to adults with a typical age of onset (Sax et al., 1997). Indeed, youth with early onset bipolar with a lifetime history of psychotic symptoms were more likely to have suicidal ideation and plans when compared to bipolar youth without psychosis (Caetano et al., 2006). Further, a recent landmark clinical trial of antipsychotic medication for early onset schizophrenia spectrum disorders reported higher than expected rates of suicidality and self-injurious behavior in their sample even after participants considered at acute risk for suicide were excluded from the study (McClellan et al., 2007). These data suggest the possibility of higher rates of such behavior in community settings where ongoing monitoring of symptoms is likely to be less structured and intensive as within a clinical trial. Additionally, psychotic symptoms are also associated with violence against others in childhood and adulthood (Arseneault et al., 2003; Kemph, Braley, & Ciotola 1998). It is therefore not uncommon for youth with EOP to interface with juvenile justice systems (Cepeda, 2007).

Conclusions about the phenomenology of EOP

Examined together, it is clear that psychotic symptoms in clinically referred youth are more prevalent than commonly thought, especially among adolescents. Data on the clinical, neurocognitive, and psychosocial correlates of psychosis in childhood and adolescence underscore how these symptoms affect *multiple* domains of functioning for the developing child, with psychotic symptoms likely to have significant adverse effects on development even outside of a well-defined schizophrenia spectrum illness (Gerralda, 1984; Hlastala & McClellan, 2005; Stayer, Sporn, & Gogtay, 2005). Psychotic symptoms in childhood and adolescence are associated with a variety of pernicious consequences that affect not only

concurrent quality of life and functioning but which are also likely to alter developmental trajectories and thus have a marked impact on future functioning as well.

Indeed, a critical dimension of EOP is their longitudinal course, specifically, how an early onset of psychotic disorder affects long-term clinical and functional outcomes, and how key clinical variables may change over time. The longitudinal course of psychotic disorders in childhood and adolescence has only been investigated to a limited extent, especially relative to available data on adult populations. Longitudinal studies have, however, helped identify meaningful variations in illness course among the childhood psychoses. I will next summarize the extant literature on the course of early-onset psychotic disorders, with a focus on early onset schizophrenia spectrum illness (i.e., schizophrenia, schizoaffective disorder) and affective psychoses (i.e., major depressive disorder and bipolar disorder with psychosis). I have focused on longitudinal studies of these particular youth for both theoretical and empirical reasons.

First, the theoretical perspective of developmental psychopathology emphasizes psychopathology as an outcome of development rather than a disease entity per se (Sroufe, 1997; Cummings, Davies & Campbell, 2000). Within this model, prior adaptation interacts with current situations to predict future functioning, thus the influence of risk factors on long term illness course is best described within a longitudinal framework. A longitudinal perspective may be particularly critical for EOP given the neurodevelopmental nature of psychotic illness in which symptoms gradually unfold over time (Rapoport & Inoff-Germain, 2000; Schaeffer & Ross, 2002).

Second, there are very few prospective studies of youth with psychotic symptoms in varying diagnostic contexts (i.e., schizophrenia spectrum illness and affective disorders with psychosis) as compared to the rare childhood-onset schizophrenia. Moreover, the statistical analyses and methodology of these studies have been limited in important ways (McClellan,

McCurry, Snell, & DuBose, 1999; Werry & McClellan, 1992; Werry, McClellan, & Chard, 1991), as I will later review. Prospective studies of youth with psychosis in varying diagnostic contexts have the potential to generate results with greater generalizability to other clinical populations, as well as to better characterize features of illness presentation that distinguish these groups (McClellan & McCurry, 1999). Such information is critical to facilitate what tends to be a complex differential diagnosis (Cepeda, 2007; Semper & McClellan, 2003) which when incorrectly applied may result in unnecessary neuroleptic treatment and missed opportunities for more targeted intervention. Thus, additional study of these groups is empirically indicated.

Longitudinal studies of the early onset psychotic disorders

Early onset schizophrenia spectrum disorder

Most long-term follow-up studies of psychotic disorders in youth have focused on early onset schizophrenia spectrum disorders (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder) which represent much less common childhood diagnoses. Follow-up outcomes have been assessed after 1-2 years (McClellan et al., 1999; Remschmidt, Martin, Schulz, Gutenbrunner, & Fleischhaker, 1991), approximately 5-7 years (Asarnow & Tompson, 1999; McClellan et al., 1993; Werry & McClellan, 1992), and 15 to 42 years (Eggers, 1978; Eggers, Bunk, Volberg, & Ropcke, 1999; Hollis, 2000; Maziade, Bouchard, Gingras, & al., 1996; Remschmidt et al., 2007; Ropcke & Eggers, 2005). Examined as a whole, longitudinal studies of childhood- and adolescent-onset schizophrenia spectrum disorders demonstrate the poorer long-term outcome of affected youth than those with an adult-onset, including high rates of chronic impairment and functional disability (Eggers, 1978; Eggers & Bunk, 1997; Eggers et al., 1999; Green, 1992; Hollis, 2000; Jarbin, Ott, & von Knorring, 2003; Maziade et al., 1996; McClellan et al., 1999; McClellan et al., 1993; Remschmidt et al., 2007; Ropcke & Eggers, 2005; Werry, McClellan, Andrews, & Ham, 1994; Werry et al., 1991). Outcome is most commonly

defined in the foregoing studies as level of psychopathological symptoms (i.e. positive and negative symptoms), and psychosocial adaptation and functioning (i.e., domains such as working behavior, employment, global social adaptation).

Very few studies have evaluated predictors of illness course but among those which have, well replicated predictors of poor clinical outcome among youth with early onset schizophrenia spectrum illness include insidious onset (i.e., a gradual, non-acute illness emergence) (Eggers & Bunk, 1997; McClellan et al., 1999; Ropcke & Eggers, 2005), lower level of premorbid adaptive functioning (Maziade et al., 1996; McClellan & McCurry, 1999; Remschmidt et al., 1991; Werry & McClellan, 1992), more severe negative and positive symptoms (Maziade et al., 1996; McClellan et al., 2003; McClellan et al., 1999), and lower cognitive functioning, usually defined by IQ (Jarbin et al., 2003; Remschmidt et al., 1991; Werry & McClellan, 1992). Findings about the predictive role of age of onset are equivocal, with some studies suggesting that an onset of illness prior to age 12 predicts a more severe course (Eggers & Bunk, 1997; Eggers et al., 1999) and others failing to find this association (Maziade et al., 1996; Werry & McClellan, 1992). When defined using current diagnostic criteria, schizoaffective disorder has been associated with the poorest outcome when compared with other early onset psychotic disorders (McClellan et al., 1999; Werry & McClellan, 1992).

Early onset affective psychoses: major depressive and bipolar disorder

Although affective disorders with psychotic features represent the most common idiopathic psychotic disorder in childhood (Cepeda, 2007), information on their longitudinal course is relatively limited. When compared with youth with early onset schizophrenia spectrum illness, youth with early onset affective psychoses have a more episodic and benign course of illness over time with periods of symptomatic and syndromal recovery (Jarbin et al., 2003; McClellan et al., 1999; Werry et al., 1991). Youth with affective psychoses generally show better overall

psychosocial functioning than those with early onset schizophrenia spectrum illness (Jarbin et al., 2003). These differences are relative, however, as early onset bipolar is characterized by a more severe symptom presentation when compared to those with an onset in adulthood, including greater suicidality, more comorbid behavioral disorders, and a larger proportion experiencing positive psychotic symptoms (Carlson et al., 2000; Sax et al., 1997).

Most available data on the prospective course of early onset affective disorders includes youth with and without psychotic symptoms, with psychosis most frequently examined as a predictor of illness course. Indeed, psychosis is among the most consistent longitudinal predictors of poorer illness course in early onset bipolar disorder, with psychotic youth more likely to have more rapid mood changes and more time with active mood symptoms (Birmaher et al., 2006; Geller, Tillman, Craney, & Bolhofner, 2004; Pavuluri, Birmaher, & Naylor, 2005). However, not all prospective studies have found an association between psychosis and severity of illness course in early onset bipolar disorder (DelBello, Hanseman, Adler, Fleck, & Strakowski, 2007). In addition to psychosis, early age of onset, family psychopathology, and mixed- or rapid-cycling episodes have been associated with worse longitudinal course (Birmaher et al., 2006; Geller et al., 2004; Pavuluri et al., 2005). It is therefore likely that the worse illness course observed among youth with bipolar disorder with psychotic features reflects interactions between these variables and psychotic symptoms (Birmaher et al., 2006; Carlson, Bromer, Driessens, Mojtabai, & Schwartz, 2002).

There is extremely limited prospective, longitudinal information on psychotic symptoms within early onset major depressive disorder. There is evidence that psychotic features among children and adolescents with major depressive disorder predicts the later development of bipolar disorder, although data are limited (Geller, Fox, & Clark, 1994; Strober & Carlson, 1982).

Conclusions about the longitudinal course of EOP

Overall, long-term symptomatic and functional outcomes are particularly severe among youth with early onset schizophrenia spectrum disorders. The most consistent predictors of more severe clinical and functional outcomes among these youth include worse premorbid adaptive functioning, lower IQ, more severe negative symptoms, and an insidious onset. The well replicated prognostic value of premorbid functioning on illness course is consistent with theories of developmental psychopathology that emphasize the influence of prior adaptation on subsequent development (Cummings, Davies, & Campbell, 2000), illustrating the importance of this perspective in the evaluation of illness course. However, the specific kinds of premorbid abnormalities may have distinct predictive effects on illness course (i.e., non-psychotic behavioral disturbances versus adaptive problems primary to psychotic illness) and thus potentially represent distinct subtypes of affected youth (Maziade et al., 1996). Such differences indicate the importance of the continued evaluation of predictors of illness course.

With respect to affective psychoses, course of illness appears more episodic than chronic when compared with early onset schizophrenia spectrum disorders, with frequent periods of symptomatic and syndromal recovery. Although many youth with early onset affective psychoses will remain functionally impaired despite symptomatic improvement, studies suggest superior functional outcomes among those with early onset affective psychoses relative to youth with schizophrenia spectrum illnesses. The predictive effects of psychotic symptoms within early onset bipolar illness is to some degree an unsettled question as prospective data continue to emerge, with varying results likely due in part to methodological differences in studies. Finally, there remains extremely limited information on the prospective course of psychotic symptoms in early onset affective disorders, and a particular paucity of data on psychosis within major depressive disorder.

The longitudinal literature on early onset psychotic disorders: Methodological critique

Conclusions based on the foregoing review of extant longitudinal studies are tempered by multiple methodological and statistical limitations that require careful review to inform interpretation as well as introduce the current study. Limitations exist in the following categories: study methodology and design, statistical techniques, inattention to potentially modifiable variables, and limited study of youth with EOP in varying diagnostic contexts.

Methodology and design

Methodological limitations of the extant longitudinal and follow-up literature include retrospective designs (Eggers & Bunk, 1997; Eggers et al., 1999; Hollis, 2000; Jarbin et al., 2003; McClellan et al., 1993; McShane, M., G., & Rey, 2006), lack of standardized outcome measures at baseline and during the follow-up period (Werry & McClellan, 1992), and misdiagnosis or the lack of structured, standardized diagnostic interview assessments (Eggers & Bunk, 1997; Eggers, Bunk, & Krause, 2000; Eggers et al., 1999; Hollis, 2000; Jarbin et al., 2003; McClellan et al., 1993; McShane et al., 2006; Ropcke & Eggers, 2005; Werry et al., 1991).

The vast majority of the available research on the course of EOP consists of *ad hoc* retrospective studies which are plagued by many limitations, including the reliance on chart review to generate diagnostic and predictor criteria, and unknown reliability of data capture (Merry & Werry, 2001). Thus, the need for prospective studies among youth with EOP is great. Prospective studies permit a rigorous characterization of diagnostic status at baseline, the absence of which is a significant limitation of extant studies. Indeed, the common use of retrospective diagnosis based on chart review, medical records, or symptom check-lists rather than standardized diagnostic interviews is especially problematic. The diagnosis of EOP is often extremely complex, especially determining whether observed psychotic symptoms reflect a primarily psychotic or mood disorder (Calderoni et al., 2001; Carlson, 1990; McKenna, Gordon, Lenane, & Kaysen, 1994; Reimherr & McClellan, 2004). The potential for retrospective chart

data to generate large numbers of "false positive" diagnoses for childhood-onset schizophrenia has been demonstrated in many studies, underscoring the importance of in-person diagnostic evaluation (Jacobsen & Rapoport, 1998; Kumra et al., 1998; McKenna et al., 1994). Thus, a significant portion of the longitudinal literature on EOP follows youth for whom diagnosis and precise illness characterization is unclear and/or retrospectively determined. This greatly limits the validity and generalizability of available findings (McClellan, 1999).

The current study rigorously evaluated all participants based on in-person and standardized diagnostic interviews which have been shown to significantly enhance the validity of diagnoses for youth with EOP (Calderoni et al., 2001; McKenna et al., 1994). Because the majority of available data on the long-term course of EOP is based on retrospective designs, the prospective characterization of participants using such procedures is a considerable strength of the proposed study.

Statistical techniques

In addition to the foregoing review of methodological limitations, statistical analyses within past longitudinal studies represent another important limitation of the extant literature. Specifically, the overwhelming majority of previous longitudinal studies have limited their analyses to frequency statistics and other descriptive techniques (e.g., ANOVA, correlation analysis) to characterize outcome and course (Asarnow et al., 1994; 1999; Eggers et al., 1989, 1999, 2000; Remschmidt, 2007). Many of these studies are also limited to one follow-up point (Eggers et al., 1997, 1999, 2000; McClellan & McCurry, 1999; Remschmidt, 2007).

The few studies which have applied multivariate techniques to longitudinal data on EOP have utilized fixed-effects regression and repeated measures analysis of variance to analyze repeated measures data (McClellan, McCurry, Snell & DuBose, 1999; Ropcke & Eggers). The application of standard multivariate models to longitudinal data ignores the hierarchical, or

nested, structure of repeated measures data. Specifically, repeated sampling of the same individuals over time creates within-person correlations which traditional analytic methods ignore. The consequences of ignoring the nested structure of repeated measures data include inflated test statistics and limited standard error estimates, increasing the possibility of Type I error, concluding effects exist that do not (Bauer & Curran, 2006; Dunlop, 1994; Raudenbush, 2002). The current study will utilize analytic techniques which avoid these statistical limitations techniques (i.e., hierarchical linear modeling) which permit an analysis of illness course that has not to date been undertaken.

Inattention to potentially modifiable variables

Another limitation of the available longitudinal literature on EOP is its relative inattention to variables associated with illness course that are potentially modifiable with adjunctive psychological treatment (Miklowitz & Hooley, 1998). The most well studied predictors of longitudinal illness course in EOP are fixed aspects of illness presentation, such as age of onset and premorbid functioning. Although such features of illness presentation help identify those at highest need for adjunctive treatment and characterize differences among the childhood psychoses, they are impossible to modify with psychological intervention. To date, the predictive effect of potentially modifiable variables on long-term illness course has not been evaluated among youth with EOP.

One such variable is medication adherence. Although this has not been studied among children and adolescents with EOP it is one of the most significant longitudinal predictors of relapse among young adults early in psychotic illness (Gitlin et al., 2001; Robinson et al., 1999). The chronic nature of EOP means that affected youth may require long-term antipsychotic treatment to manage their symptoms and during adolescence may assume greater control over their medications as is developmentally appropriate. It is therefore widely agreed that non-

adherence and factors predisposing individuals to be non-adherent (e.g., side effects, cognitive difficulties) be key targets of treatment, particularly early in psychotic illness (Coldham, Addington, & Addington, 2002; Gray, Wykes, & Gournay, 2002). To date, this construct has not been studied in a longitudinal context among EOP thus its preliminary exploration in the proposed study is a first step in understanding this construct among affected youth.

Limited follow-up data on youth with EOP in varying diagnostic contexts

As previously reviewed, the majority of EOP follow-up studies report only on youth with an onset of schizophrenia prior to age 12 or 13, a much rarer child population. Other prospective studies follow youth with atypical psychotic presentations (i.e., initial diagnoses of psychotic disorder not otherwise specified) (Nicolson, Lenane, & Brookner, 2001). These youth, while often severely impaired at baseline and long-term follow-up, show poor diagnostic stability over time (Schwartz et al., 2000; Srinath, Janardhan, Girimaji, & Seshadri, 1997) and tend not to develop schizophrenia spectrum disorders. Importantly, such youth present with unique therapeutic needs related more to emotion dysregulation and behavioral disorders rather than psychotic symptoms per se (Hlastala & McClellan, 2005; Stayer, Sporn, Gogtay et al., 2005). Thus, these youth appear to represent a related but distinct population.

Prospective studies of youth with EOP in varying diagnostic contexts have the potential to generate meaningful information about differences in course based on results with greater generalizability to clinical populations. There are few published prospective, longitudinal studies of youth rigorously diagnosed at baseline with EOP in varying diagnostic contexts (Castro-Fornieles et al., 2007; McClellan & McCurry, 1999; McClellan et al., 1999; Werry & McClellan, 1992; Werry et al., 1991). Thus, although available prospective studies have generated meaningful information on the long-term course of EOP, none have not accounted for the nested structure of repeated measures data in their analyses, examined potentially modifiable

predictors of illness course, or described the effects of initial medication response on long-term clinical outcomes.

Examined together, there is extremely limited prospective, longitudinal data available on youth with rigorously characterized EOP in multiple diagnostic contexts and for whom medication response data is available. These youth represent a distinct clinical population in whom risk factors associated with a more pernicious course of illness have only been studied to a limited extent. From a clinical perspective, it may be that the limited quantity and methodological limitations of the available literature on EOP has helped forestall the development and evaluation of adjunctive psychological treatments that are so sorely needed for this impaired population.[1] Indeed, because developmental factors such as age, stage of illness, and cognitive and emotional capacities affect symptom presentation and may moderate illness course and treatment responsiveness (Eyberg, Schuhmann, & Rey, 1998; Weisz & Hawley, 2002), their characterization is essential to future applied research. Specifically, it is currently recommended that basic research on the phenomenology and longitudinal course of illness represents a critical foundation of intervention research with children and adolescents (Shirk, 1999; Weisz & Weersing, 1999) to help avoid the historically commonplace but developmentally problematic downward adaptation of efficacious adult interventions to adolescent and then school-aged populations (Kazdin & Kendall, 1998; National Advisory Mental Health Council's Workgroup on Child and Adolescent Mental Health Intervention, 2001).

Accordingly, the current study aims to characterize and evaluate risk factors longitudinally

[1] The empirical literature on treatment for EOP is remarkably limited relative to the magnitude of impairments associated with these illnesses, especially when compared to the far more developed treatment literature for adults with the same illnesses (Penn, Waldheter, Perkins, Mueser, & Lieberman, 2005; Turkington, Kingdon, & Weiden, 2006). With respect to pharmacotherapy, there have been ten clinical trials of second-generation antipsychotic medications for children and adolescents with EOP which suggest unique developmental effects of these agents on youth (for a review, see Kumra et al., 2008. There have been no clinical trials of adjunctive psychological interventions for children with EOP and their families. For adolescents, there have been only pilot studies and open trials of a group therapy intervention for auditory hallucinations and cognitive remediation-based treatments (Jenner, 2001; Newton, Landau, & Smith, 2005; Ueland & Rund, 2005).

associated with illness course and to complement the available literature on the longitudinal course of EOP which suggests meaningful variations in illness course but whose conclusions are limited by multiple methodological and statistical limitations. In turn, future investigations may then evaluate processes by which such factors causally relate to outcomes in order to inform treatment development.

The current study utilized a longitudinal dataset on the prospective course of early onset psychotic illness that monitored youth following their participation in one of three controlled trials of antipsychotic treatment. Analyses aimed to characterize risk factors associated with a more severe illness course and evaluated the strength of these predictors in this understudied child and adolescent population. To accomplish these aims, the current study examined the following hypotheses.

Hypothesis 1 evaluated predictors of clinical outcome. I hypothesized that lower baseline IQ, an earlier onset of psychotic symptoms, medication nonadherence, and a failure to respond to antipsychotic medication would predict higher levels of positive and negative symptoms and overall psychiatric symptoms during the follow-up period. The previously reviewed literature on predictors of long term illness course in EOP, including age of onset and IQ (Eggers & Bunk, 1997; Eggers et al., 1999; Jarbin et al., 2003; Werry & McClellan, 1992), the theoretical importance of early adaptation informing subsequent development (Sroufe, 1997; Sroufe & Rutter, 1984) and the need to better understand the effects of medication adherence and response on illness course provide empirical and conceptual support for this hypothesis.

Hypothesis 2 evaluated the relationship between illness course and these risk factors utilizing distinct analytic techniques. Based on *a priori* criteria, I divided my sample into two groups based on change in symptoms over the study's follow-up period: improved and not improved. I then evaluated whether these outcome groups predicted the variable set evaluated in

Hypothesis 1 (i.e., age of onset, medication nonadherence, lower IQ, medication response). These analyses will identify what outcome group accounts for most variance in the risk factors.

Importantly, the focus of the current study is the descriptive identification of risk factors associated with a more severe illness course; the evaluation of etiological processes related to illness progression is beyond its scope. It is nevertheless essential that risk factors be prospectively examined using appropriate statistical techniques in order for future research to identify the processes by which these variables confer risk (Cowan, Cowan, & Schulz, 1996) and thus be of greatest utility within future treatment research (Shirk, 1999; Weisz & Hawley, 2002).

CHAPTER 2

METHODS

The current study uses data from a grant-supported investigation called the Long Term Course Study (LTC), a prospective, longitudinal study of children and adolescents with early onset psychotic disorders. These data were collected by Sikich and colleagues (Sikich, Sheitman, & Lieberman). The LTC followed a sample of youth with rigorously characterized early onset psychotic disorder for 1-5 years following their participation in one of three initial antipsychotic medication trials. The LTC study is an observational, prospective follow-up study that aimed to provide information about the long-term course of a subgroup of youth with psychotic disorders who were treated with antipsychotic medication during the initial medication trials.

Original Medication Trials

Participants in the LTC study include children and adolescents who originally participated in one of three initial industry-sponsored (i.e., Ziprasidone for Early Onset Schizophrenia Spectrum Disorders, ZEOSS) or National Institute of Mental Health (NIMH) sponsored controlled trials (i.e., Treatment of Adolescent Psychosis, TAPS; Treatment of Early Onset Schizophrenia Spectrum Disorders, TEOSS). The first treatment study, TAPS, was a double-blind, three arm comparison of haloperidol, risperidone, and olanzapine among children and adolescents with active psychotic symptoms occurring in the context of schizophrenia spectrum disorders or major affective psychotic disorder (n=50)(Sikich, Hamer, Bashford, Sheitman, & Lieberman, 2004). Participation in the TAPS trial ranged from 3 weeks to 13 months. The second treatment study, TEOSS, was a multisite randomized, double blind efficacy study

comparing the efficacy and tolerability of three atypical antipsychotic medications, molindone, risperidone and olanzapine, in children and adolescents with schizophrenia spectrum disorders (*n*=119 across sites; UNC *n*=44) (Frazier et al., 2007; McClellan et al., 2007). The third treatment study, ZEOSS, was a multi-site, industry-sponsored study evaluating the efficacy and tolerability of the antipsychotic medication ziprasidone (*n*=40 across sites; UNC *n*=14).

Thus, all participants in the LTC Study originally participated in the original TAPS, TEOSS, or ZEOSS investigations (flow of participants from the original treatment studies to the Long Term Course investigation is shown in Figure 1).

Subjects were between 8 and 19 years of age when initially characterized for the TEOSS, ZEOSS or TAPS treatment studies. There were no exclusions for gender or ethnicity, although individuals with psychotic symptoms secondary to substance use and those with IQs less than 65 were excluded. Criteria for participation in the initial medication trials and subsequent enrollment in LTC are as follows.

TAPS participants were required to have had active psychotic symptoms that were at least moderately severe (as defined by a score of "4" or more on at least one of the psychotic items of the Brief Psychiatric Rating Scale for Children (BPRS-C)), and a primary diagnosis of either a schizophrenia spectrum disorder or an affective psychotic disorder (i.e., major depression or bipolar disorder with psychotic features).

TEOSS and ZEOSS participants had similar requirements for active psychotic symptoms of at least moderate severity (defined with the PANSS), but were required to have a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder (Frazier et al., 2007; McClellan et al., 2007). Youth with affective psychosis were excluded from these studies.

The inclusion criterion for **Long Term Course** was prior enrollment in TAPS, ZEOSS, or TEOSS, with no additional exclusionary criteria. Thus, these studies shared similar inclusion

criteria with the exception of TAPS which enrolled youth with schizophrenia spectrum illnesses and affective disorders with psychosis.

As a result, diagnostic composition of participants of the initial treatment studies varied somewhat. Specifically, youth with affective disorders with psychosis were enrolled in TAPS but only youth with schizophrenia spectrum disorders participated in TEOSS and ZEOSS. As previously reviewed, differences in illness severity and course among these diagnostic groups are not well characterized in child populations but those reported may inform differences in study results. Accordingly, baseline demographic and clinical characteristics for the four diagnostic groups (i.e., schizophrenia, schizoaffective disorder, major depression with psychosis, bipolar disorder with psychosis) were descriptively analyzed and are presented in Table 1. One way ANOVAs were performed for continuous variables and chi-square analyses for categorical data.

Overall, there were some significant differences observed among the diagnostic groups. With respect to demographic characteristics, there were significant differences in the proportion of gender across diagnoses. Clinically, there were significant differences in baseline IQ based on diagnostic status (F=23.5; p=.00), with differences in the expected direction (i.e., schizoaffective<schizophrenia<major depression<bipolar disorder). There were also significant differences in age of onset of psychotic symptoms (F=3.09; p=.04) with bipolar youth having the oldest age of symptom onset and youth with schizoaffective disorder the youngest (sza<mdd<sz<bpd).

With respect to the primary outcome measures, there were significant baseline differences in psychotic symptoms as measured by the PANSS total score between youth with schizophrenia and schizoaffective disorder with youth with schizophrenia having higher levels of baseline psychotic symptoms than youth with schizoaffective disorder. There were no significant differences in baseline levels of general psychiatric symptoms as measured by the BPRS-C total

score, with trends of overall symptom level somewhat different with youth with bipolar disorder showing the highest levels of general psychiatric symptoms (i.e., bpd>sz>mdd>sza).

Participants in the current study

There are 38 individuals followed for the Long Term Course study with at least 2 years of data available for analysis. Demographic and clinical characteristics of the study sample are presented in Table 2. The average period of follow-up is 3.3 years (range: 1 year, 5 months – 7 years, 5 months), and the mean number of assessments per individual is 3 (SD: 3.0; range 1-8). The mean age at entry into initial medication trials is 13 (SD: 2.8; range 8-19). The ethnic composition of the sample is as follows: 73.7% are non-Hispanic White (*n*=28), 18.4% are non-Hispanic Black (n=18.4%), 2.6% are Hispanic (*n*=1), 2.6% (*n*=1) are American Indian and 2.6% (*n*=1) identified as other or not specified.

Socioeconomic status was assessed within the original TAPS study using Hollingshead education and occupation codes (Hollingshead, 1957). The most common highest level of education among parents of TAPS participants was high school graduate (35%), with 24% having parents with some graduate/professional school, 18% reporting partial college, 18% college graduates, and 5% junior high school. Socioeconomic status was determined for youth originally enrolled in TEOSS based on household income level. There was a range of household incomes observed among these youth (25%= <$20,000; 25%=$20-40,000; 25%= $40-60,000; 17%=$60-80,000; 8%=$80-100,000).

With respect to the sample's gender composition, fifty-five percent of participants are male (*n*=21). Subjects were psychotic for an average of 2.2 years prior to enrollment in the original medication trials and 60% were experiencing their first episode of psychosis upon their enrollment. Mean age for the initial onset of psychotic symptoms was 11.3 (SD: 3.2) (range 3-17). Fifty-eight percent (*n*=22) of participants had a childhood-onset of psychotic illness (i.e.,

onset at or prior to age 12) and 42% (*n*=16) had an adolescent-onset (i.e., 13 years or older). Baseline diagnoses were as follows: 36.8% schizophrenia (*n*=14), 18.4% schizoaffective disorder (*n*=7), 18.4% bipolar (*n*=7), 26.3% major depressive disorder (*n*=10).

In terms of baseline clinical status, the overall sample's average level of psychotic symptoms is quite high, with a mean PANSS total score of 98.7 (SD: 18.84; range 72-138) (Table 2). These values exceed the published means for this measure (Kay, Fiszbein, & Opler, 1987) although these means are based on adults with chronic schizophrenia. Baseline data on psychotic symptoms presented in Table 2 reflect youth originally enrolled in TEOSS only, as baseline PANSS data was not collected on youth originally enrolled in TAPS. With respect to general psychiatric symptoms, the overall sample is highly symptomatic with a mean total BPRS-C score of 47.2 (SD: 9.7; range 31-74). This well exceeds the total mean score of the diagnostically heterogeneous sample of clinically referred youth who comprised the measure's validation sample (mean score=27.8) and approximates the mean of the sample's subset of youth with psychotic disorders (mean=49) (Lachar et al., 2001; Overall & Pfefferbaum, 1982).

The mean number of prior hospitalizations upon entry to the Long Term Course study is 1.3 (SD: 1.4; range 0-5), and 29% (*n*=11) of participants had repeated a grade in school and the sample received an average of 1.84 (SD: 1.65; range 0-6) prior diagnoses. The degree to which these prior diagnoses reflect true psychiatric comorbidity and/or early neurodevelopmental manifestations of emerging psychotic disorder is unclear (Schaffer & Ross, 2002). Overall, however, descriptive data and baseline clinical characteristics suggest significant morbidity within the study sample.

Design and Procedure

After completing one of three initial medication trials, youth who responded to medication were followed to determine the incidence of relapse, and youth who did not respond to the

study medication were followed to determine the ongoing course of illness (i.e., no change, worsening, or improvement). Subjects were to be assessed in person at 4-6 month intervals to evaluate their psychiatric status, particularly with regard to exacerbations or relapses during the interval since their last evaluation, and the level of psychotic symptoms. A clinical social worker and/or child psychiatrist, each with extensive clinical experience with this population, collected all follow-up data based on in-person interviews including biological measures of safety and tolerability and measures of psychiatric symptomatology. Data on adherence to prescribed medications during follow-up intervals was also collected, and baseline IQ data are available from the original medication trials in which youth participated.

Measures

Diagnosis. At baseline, all subjects met DSM-IV (APA, 1994) diagnostic criteria for schizophrenia, schizoaffective disorder, bipolar affective disorder with psychotic features or major depression with psychotic features, as determined by medical record review, detailed clinical evaluation by a child psychiatrist, and a structured diagnostic interview. These interviews included the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS-P)(Chambers, 1985) within the TAPS study, and the KID-SCID (Hien, Matzner, Spitzer, Gibbon, & Williams, 1998) within TEOSS. The Structured Clinical Interview for DSM-IV (SCID) (First, Gibbon, Spitzer, & Williams, 1997) is widely used in schizophrenia literature, and the KID-SCID is adapted from this. The KID-SCID includes modules to assess childhood psychiatric disorders, and the mood, psychosis, and substance abuse modules found in the adult version. Both structured diagnostic interviews are designed to supplement and corroborate clinical evaluations performed by experienced child psychiatrists and to yield diagnoses consistent with DSM-IV criteria. Diagnosticians were child psychiatrists, social workers, or psychiatric nurse specialists with extensive child psychiatry experience. All diagnosticians

achieved high inter-rater reliability (i.e., kappa ≥ .85) on both diagnostic instruments throughout the study period. Subjects with a DSM-IV diagnosis of bipolar affective disorder or major depressive disorder with psychotic features had persistent psychotic symptoms despite at least four weeks of appropriate treatment with mood stabilizing agents.

Medication response: Response to medication during the original medication trials (i.e., TAPS, TEOSS) was determined dichotomously (i.e., response, no response) based on *a priori* criteria commonly utilized in child and adolescent psychopharmacology research. Specifically, response to antipsychotic treatment in TAPS was defined as a 20% or more reduction in psychotic symptoms based on the Brief Psychiatric Rating Scale for Children (BPRS-C) (Overall & Pfefferbaum, 1982) from baseline to the end of the trial's 8-week acute phase (Sikich et al., 2004). In TEOSS, responder status required a 20% or more reduction in the baseline Positive and Negative Symptom Scale score (PANSS) (Kay et al., 1987) after the first 8 weeks of treatment.

Psychotic symptoms: The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is a 30-item, clinician-rated scale focused on psychotic symptoms widely used in the adult literature. It was administered at baseline for TEOSS and ZEOSS participants and at each follow-up assessment during participation in Long Term Course. The PANSS has established internal consistency on each of its three subscales, with coefficient alphas of 0.83, 0.73, and 0.79 for the negative, positive, and general psychopathology scales, respectively (Kay et al., 1987; Kay, Opler, & Fiszbein, 1986). Clinicians rate individual symptom items based on a 7-point scale ranging from "1" for absent and "7" for extreme. The PANSS was selected because it provides a more comprehensive assessment of psychotic symptoms than any scale designed for children. It further provides continuity with adult schizophrenia studies. Interrater reliability on the PANSS was attained among study staff at an intraclass correlation coefficient of at least 0.80.

Psychiatric symptoms: The Brief Psychiatric Rating Scale for Children (BPRS-C) (Overall & Pfefferbaum, 1982) is a 21-item, clinician-rated measure of psychiatric and behavioral problems commonly observed in children and adolescents receiving psychiatric treatment. Clinicians rate individual symptom items based on a 7-point scale ranging from "0" for not present and "6" for extremely severe. The BPRS-C has established internal consistency on each of its seven factor scores (i.e., behavioral problems, depression, thinking disturbance, psychomotor agitation, withdrawal, anxiety, organicity), with coefficient alphas ranging from .689 - .906). It was selected for continuity with the adult literature (BPRS) (Overall & Gorham, 1962) and because it is considered an appropriate tool for longitudinal follow-up within a naturalistic design (Gale, Pfefferbaum, Suhr, & Overall, 1986; Lachar et al., 2001). The BPRS-C total score will be used as a primary outcome as it more comprehensively captures the range of behavioral problems seen in youth with EOP than the thinking disturbance and withdrawal subscales do (McClellan, McCurry, Speltz, & Jones, 2002). Interrater reliability was attained on the BPRS-C at an intraclass correlation coefficient of at least 0.80.

Age of onset: Age of onset of psychotic symptoms was determined upon enrollment to the original medication trials (i.e., TAPS, ZEOSS, TEOSS) based on clinical interview and evaluation by child psychiatrists with extensive experience with this population. Childhood-onset of schizophrenia is defined in the literature as onset of illness at or prior to age 12 and adolescent-onset as 13-19 years of age (Gillberg, 2001). Age was kept continuous within analyses and interpreted accordingly.

Medication adherence: Adherence during the original medication trials (i.e., TAPS, ZEOSS, TEOSS) was assessed by pill counts, a rigorous means for evaluating adherence (Farmer, 1999). During the follow-up period of the Long Term Course study, medication adherence was assessed by self-report. Specifically, study staff asked participants if he/she "takes his/her

medication regularly." Responses were binary: "yes" or "no." I created a dichotomous variable based on aggregate adherence ratings for each participant where an individual was considered adherent if they report "yes" to the medication adherence question 75% or more of the time. Participants who report "no" less than 75% of the time was considered non-adherent. These cut-offs are based on a precedent for dichotomizing self-report adherence data within the schizophrenia literature (Bachmann, Bottmer, & Schroder, 2005; Sibitz, Katschnig, Goessler, Unger, & Amering, 2005), and use of this percentage value to validly capture adherence (Adams & Scott, 2000; Arango, Bombin, Gonzalez-Salvador, Garcia-Cabeza, & Bobes, 2006; Donohoe et al., 2001). There is no "gold standard" of medication adherence for pediatric populations (La Greca & Schuman, 1995), and self-report was selected in part to decrease staff and participant burden, which is of particular importance in longitudinal designs. Because self-report adherence data in schizophrenia research tend to *overestimate* adherence (Velligan et al., 2006), this variable will be evaluated in an exploratory manner and results interpreted cautiously.

Cognitive functioning was assessed upon enrollment to the original medication trials as well as during the follow-up period. The current analyses will utilize participants' baseline IQ to provide a proxy measure of premorbid functioning based on precedent within the adult schizophrenia literature (DeQuardo, Goldman, Tandon, McGrath-Giroux, & Kim, 1995; Greenwald, Harder, Gift, & Strauss, 1989). In TAPS, IQ was established using the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III) (Weschler, 1991) or the Wechsler Adult Intelligence Scale, Revised (WAIS-R) (Weschler, 1981) (for youth 17 years or older). Within TEOSS and ZEOSS, IQ was established using the Wechsler Abbreviated Scale for Intelligence (WASI) (Wechsler, 1999). Both tests provide a measure of verbal and nonverbal reasoning, and are widely used in neuropsychological research as a measure of global cognitive functioning. Scales were administered by a masters-level clinician and results were interpreted by the study's child

neuropsychologist. IQ is a continuous variable and was analyzed accordingly.

Improved course. Groups reflecting "improved" and "not improved" illness were formed based on a priori criteria. Specifically, youth were considered improved if a 20% or more reduction in psychiatric symptoms, as measured by the BPRS-C total score, as observed from baseline to their final follow-up visit. Youth were considered not improved if this 20% reduction was not observed. This grouping strategy was selected for several reasons, including continuity with the adult psychotic disorders literature in which a 20% reduction in PANSS is an established convention for clinically meaningfully change in psychotic symptoms (Cather et al., 2005). Second, a 20% reduction in BPRS-C is widely used to characterize treatment response and symptomatic change in childhood psychosis within the pharmacological literature (Lachar et al., 2001) and the description and classification of study participants (Emslie, Rush, Weinberg, Rintelmann, & Roffwarg, 1994; Pfefferbaum, Mullins, Rhoades, & McLaughlin, 1987). In addition, similar definitions of symptom change were utilized within the original medication trials on which the current study is based (Sikich et al., 2004; Frazier et al., 2007) and is therefore consistent with the original study's measurement.

CHAPTER 3

RESULTS

Descriptive Statistics

Correlations between the predictor and outcome variables are reported in Table 3. Correlations are somewhat consistent with the wider literature, with expected correlations observed between total BPRS-C and PANSS scores ($r = .76$; $p < .05$). No significant correlations were found between the primary outcome measures (i.e., BPRS-C and PANSS) and covariates except for a negative correlation between medication adherence ratings and total BPRS-C score, suggesting an association between lower ratings of medication adherence and greater symptoms ($r = -.18$; $p < .05$). Among the predictor variables, only medication adherence ratings and IQ were significantly correlated ($r = .19$; $p < .05$), suggesting an association between higher ratings of medication adherence and higher IQ.

Analytic Approach

Hypothesis 1 was examined within an HLM framework (Raudenbush, 2002), which includes techniques used to examine data reflecting a nested structure, such as repeated measures data. HLM accounts for the within-person correlations, or nonindependence, that result from repeated sampling of the same individuals over time. As previously reviewed, this type of analysis has a number of advantages, but given the limited sample size in this study there are some associated difficulties of using HLM, including the interpretation of parameter estimates. Specifically, utilizing HLM with small samples is associated with unreliable estimates of within person variance. I therefore obtained population estimates based on a sample of nested repeated

within-individual observations, where my sample size does not permit reliable estimates of within person variance. I modeled a random intercept which maintains the foregoing advantages of HLM but avoids these problems of estimation.

As applied to the current study, I evaluated a two-level model with predictors at Level 2. Within an HLM framework, Level 1 factors vary within individuals (e.g., symptom level) and Level 2 factors are fixed within person but vary between subjects (i.e., onset of illness, medication response, adherence ratings, IQ). The following HLM equation demonstrates the test of one hypothesis:

Level 1: $\gamma_{00} + \gamma_{10}\,\text{time}_{it}$

Level 2: $\gamma_{01}\text{IQ}_1 + \gamma_{02}\text{ONSET}_i + \gamma_{03}\text{RESP}_i + \gamma_{04}\text{ADHER}_i + \gamma_{05}\text{RESP}_i + \gamma_{06}\text{study}$

The random intercept parameter here is denoted as γ_{00} which indicates the amount of variance in the outcome variable associated with the predictor variable.

Before running the proposed models, I examined potential control variables (i.e., gender, ethnicity, SES measures). None were significantly related to the primary outcome measures ($p < .05$) even at a trend level ($p < .10$) and therefore were not included in subsequent analyses. Also, I evaluated possible outliers among discrete covariates prior to evaluating the models. One outlier was identified with respect to age of onset. I examined the residuals derived from the model which includes age of onset within a g-plot. The residuals appeared normal thus the outlying value is not expected to affect results (see Figure 2 for predicted values plotted against age of onset).

Missing data was evaluated and managed within the final models in the following manner. Linear mixed model estimators are robust to missing data generated from a missing at random (mar) process as long as the covariates associated with missingness are included in the model (Little & Rubin, 1987). I therefore evaluated associations between all covariates of interest and

missingness using logistic regression. None of the covariates were found to be associated with missingness and were thus not included in the model. There may be covariates I do not observe that are associated with missingness, however, I tested the set which I do possess and none of these significantly predict missingness. Any covariates I do not have access to which may predict missingness are tantamount to a person-specific effect and to some extent the random intercept I have estimated captures this, thus helping to satisfy the mar assumption. Thus, based on these analyses none of the parameter estimates and test statistics associated with these models should be biased as a function of missingness.

Also prior to running the proposed models, I evaluated the distributions of my primary outcome measures (i.e., PANSS and BPRS-C) using quantile quantile plots. Both appeared normally distributed (see Figure 3). Accordingly, I used Proc Mixed in SAS software for the prediction of continuous outcomes (i.e., PANSS and BPRS-C), using restricted normal theory maximum likelihood and the Kenward-Roger method to calculate degrees of freedom (recommended for use with small sample sizes).

Hypothesis 1

Hypothesis 1 evaluated the predictive effects of four clinically relevant risk factors (i.e., lower baseline IQ, medication nonadherence, medication non-response, and an earlier age of illness onset) on symptom levels during the follow-up period as measured by the PANSS total score and its subscales (i.e., positive, negative and general) and BPRS-C total score and its subscales (i.e., mania, behavioral problems, depression and thinking disturbance). Baseline PANSS data were only available for 14 participants because this measure was not used within one medication study (TAPS) but was used within the other two (TEOSS and ZEOSS). To address this in the model, I first evaluated differences between the two study groups (participants TAPS versus the combined TEOSS/ZEOSS sample, heretofore referred to as

TEOSS). The mean total PANSS score for TAPS youth at visit 2 was 62.91 and the mean total PANSS score for TEOSS youth at baseline was 98.71. A one-way ANOVA evaluated the difference between these two groups which was significant at the $p<.05$ level ($F = 35.79$, $p<.0002$). To correct for this in the final model I incorporated a study effect to account for all differences emanating from original study membership.

Results of these models, including fixed effects, are summarized in Tables 4 through 7. Each model included the four covariates of interest as Level 2 (i.e., IQ, medication adherence ratings, medication response, age of onset), diagnostic group, an effect for study, time as a fixed effect and a random intercept.

Change in psychotic symptoms

Results indicate that levels of psychotic symptoms decreased significantly ($B= -3.93$; $p<$ .01) as measured by the PANSS total score from baseline to the final assessment (see Table 5). Significant decreases in level of symptoms were observed in all subscales of the PANSS, including positive symptoms ($B= -1.16$; $p= .01$), negative symptoms ($B= -0.93$; $p= .01$) and general symptoms ($B= -1.91$; $p= .01$). However, results show that none of the covariates examined predicted significant variance in the observed changes (Table 4). Specifically, baseline IQ ($B= .05$; $p= .83$), age of onset ($B=.37$; $p= .78$), medication adherence ratings ($B= -2.9$; $p= .83$) and medication response within the original medication trials ($B=$ -5.6; $p= .58$) were all non-significant predictors of change in levels of psychotic symptoms (i.e., PANSS total score). In addition, these covariates were also non-significant predictors of psychotic symptom level as measured by PANSS subscales (i.e., positive symptoms, negative symptoms, general symptoms; see Table 4).

Thus, the predictive utility of baseline IQ, adherence ratings, medication response and age of onset with respect to levels of psychotic symptoms (Hypothesis 1) was not supported.

Changes in general psychiatric symptoms

Results show that levels of general psychiatric symptoms as measured by the BPRS-C total score also significantly decreased during the follow-up period (B= - 4.5, p< .01) as did the symptoms captured by each of its subscales (mania B= -.84, p< .01; behavioral problems B= -0.72, p< .01; thinking disturbance B= -1.25, p< .01; depression B= -.72, p< .01). Again, however, none of the covariates of interest (i.e., baseline IQ, age of onset, medication adherence ratings, medication response) predicted significant variance in the observed changes in general psychopathology (see Table 6).

Overall, the predicted effects of IQ, age of onset, medication adherence ratings and medication response on levels of psychotic and general psychiatric symptoms were not supported within Hypothesis 1.

Hypothesis 2

Hypothesis 2 aimed to examine the results of Hypothesis 1 in greater detail and with a distinct, more descriptive analytic approach. Specifically, the current study's modest sample size and limited number of repeated measures per subject may have prevented the detection of effects within the HLM analyses. Thus, a series of descriptive analyses were undertaken to characterize the change in symptoms and evaluate the extent to which meaningful differences are observed between subgroups of youth with a more or less improved course of illness.

To accomplish these aims, I divided the sample into two outcome groups: improved or not improved. Per convention in the literature, the definition of "improved" is a 20% or more reduction in total BPRS-C score from baseline to termination and "not improved" as those youth with less than a 20% reduction in BPRS-C score. Only participants with three or more observations were included in analysis (n=26).

A series of regression models were used to evaluate whether membership in the

"improved" or "not improved" group predicted and contributed to the variance of the four covariates evaluated in Hypothesis 1. Two of these variables are binary and non-continuous (i.e., medication adherence ratings, a no response status in initial medication trial), and using linear regression models for such variables violate important assumptions of the linear model, including normality of residuals and homoscedasticity (Agresti, 2002). Accordingly, I utilized logistic regression to evaluate these two variables. IQ and age of onset are continuous variables and I therefore evaluated whether group membership predicted low IQ and earlier onset using an ordinary least squares (OLS) regression.

Prior to running the regression analyses, assumptions of these models were evaluated, including the normality of the variables and error terms, homoscedasticity and no significant outliers. Regressions were performed with and without the outlier previously described (i.e., age of onset) and results did not change when this individual was excluded from analyses. No additional covariates were included in the regression model (e.g., gender, ethnicity) as control variables given prior examination of their relationship to the dependent measures.

Regression results show that membership in the improved outcome group did not predict a significant amount of variance in age of onset (F=1.03, p= .32) or IQ (F=.61, p= .44). However, results of the logistic regressions indicate that the odds of having better adherence ratings among those in the improved group were approximately 2 times that of non-improved youth, significant at the trend level (odds ratio=3.25 x^2=2.86, p= .09). In addition, the odds of being a medication responder among those in the improved group were 1.5 times that of non-improved youth (odds ratio=2.58, x^2=4.20, p= .04).

However, because medication responders were *defined* by a 20% reduction in BPRS-C criteria following the acute, 8-week phase of their original medication trial, it is possible that this significant effect is an artifact of how this variable was coded. Accordingly, I repeated this

logistic regression using an alternative strategy for characterizing improved course, namely the calculation of reliable change index (RCI) which is considered a more sensitive and reliable measure of clinical change than percent reductions alone (Jacobson & Truax, 1991). When the RCI classification was used to predict the odds of being a medication responder, no significant effect was found (odds ratio=.54 x^2 = .47, p= .49).[2]

In summary, regression analyses did not further characterize or explain the relationship between the covariates of interest and differences in illness course. Logistic and OLS regression failed to account for significant variance in these four covariates (i.e., IQ, age of onset, adherence ratings, medication response) as a function of illness course using two different criteria for defining improvement.

Distributions

To further understand the nature of the non-significant effects of any predictor within my analyses, I examined distributions of primary outcomes (i.e., PANSS and BPRS-C) conditional on discrete covariates (i.e., medication response and medication adherence). I conducted these analyses to evaluate whether observed results reflected non-normal distributions of outcome measures (i.e., PANSS and BPRS-C) conditionally on levels of my covariates I examined these distributions using quantile quantile plots which indicate their relative normality. This suggests that study results are not likely to reflect non-normal distributions of levels of covariates on the primary outcome measures.

[2] I reran the aforementioned OLS and logistic regressions for adherence using the Jacobson et al. (1991) RCI as the independent variable to compare the findings to those obtained using BPRS-C percent reduction. Interestingly, only one more participant was characterized differently using Jacobson's RCI rather than the BPRS-C convention, with otherwise equivalent groupings. Accordingly, regression results were unchanged when the RCI-formed groups were used as predictors in the OLS and logistic regressions.

Sensitivity Analyses

The main effect for time on levels of psychotic symptoms during the follow-up period was somewhat unexpected given the chronic nature of psychotic illness among affected youth. Moreover, none of the available covariates accounted for significant variance in the observed outcomes. I therefore undertook a series of analyses to examine what may account for these differences and help explain the current findings.

Study effects

From a design perspective, the differences in protocols for the original medication studies (i.e., medications under investigation, varying diagnostic status among participants) and the uncontrolled, observational follow-up period of Long Term Course created significant, unobserved heterogeneity that likely affected the current results. Thus, I probed the main effect of study membership for potential interactions that may refine the final model and better characterize my results.

Given the potential for medication response to influence long-term symptomatic course, I examined the mean PANSS total score for all participations based on their original study membership and medication response. With respect to youth who initially participated in TAPS (n=24), differences were observed in mean PANSS total score at baseline based on medication response (mean for responders = 65.23±30.11; mean for non-responders= 46.66 ±9.29). In contrast, mean total PANSS score among youth who originally participated in ZEOSS or TEOSS (n=14) did not vary as greatly (mean for responders=101.2±13.64; mean for non-responders=97.33±21.86). I therefore added a medication response by study interaction to the final model[3] (see Table 4).

[3] Interactions between the study effect and other covariates were explored and none predicted significant variance in the final model.

Effects of interaction

Psychotic symptoms. The presence of the medication by study interaction did not change the nonsignficant effects of the four covariates (i.e., IQ, adherence, response, age of onset) on overall levels of psychotic symptoms. In the presence of the interaction term, the main effect for time remained significant with respect to PANSS total score (*B*= -3.66; *p*=.01) and each subscale (positive: *B*= -1.11; *p*= .01); negative: *B*= -.90; *p*= .02; general: *B*= -1.77; *p*= .02). The interaction predicted positive symptoms as measured by the PANSS at a trend level (*B* = -10.10 *p*= .05) but not PANSS total score or the general and negative symptom subscales.

General psychiatric symptoms. The medication by study interaction accounted for significant variance in observed changes in the BPRS-C total score (*B*= -21.18 *p*= .02) but none of its subscales (see Table 6). The presence of the interaction did not change the effects of the original covariates of interest (i.e., IQ, age of onset, adherence ratings, medication response), all of which remained nonsignificant. The main effect of time on general psychiatric symptoms also remained significant (*B*= -4.5; *p*=.0001) in the presence of the medication response by study interaction.

Overall, results of these study effect analyses suggest that an interaction between medication response and study contributed significant variance to the observed changes in levels of general psychiatric symptoms.

To supplement my analyses of study effects, I evaluated another dimension of design in order to better characterize the significant decrease in psychotic symptoms over time as well as the significant variability observed in PANSS scores.

Rater effects

Rater bias is a form of method variance that has the potential to contribute systematic variance in observed scores that is not due to the subject (Campbell & Fiske, 1959). I evaluated the presence of rater effects to better understand the somewhat unexpected findings that

psychotic symptoms significantly decreased during the follow-up period. To evaluate rater effects, I modeled raters as a Level 1 time varying covariate with total PANSS score as a dependent measure.

There were four raters who evaluated participants in the Long Term Course study although two performed the vast majority of evaluations (93%; heretofore denoted as raters 1 and 2). Only one evaluator's ratings (rater 2) was significantly different from the criterion/gold-standard evaluator (rater 1) (B=19; p= .006). I then examined interaction between raters and time to evaluate the extent to which differences persisted over time and thus may have affected ratings during the follow-up period. Results for psychotic symptoms changed considerably when rater effects were modeled; specifically, the significant main effect for time disappeared (B=.50; p= .79) and its coefficient changed direction (i.e., negative to positive). This suggests that in the presence of this rater's effect, psychotic symptoms did *not* decrease significantly during the follow-up period (see Tables 4 and 5). In addition, a significant rater by time interaction was observed for rater 2 (B= -8.23; p= .0006), indicating that for every unit of time (i.e., study visit) this rater's mean PANSS score was approximately eight units less than the criterion rater's. These data suggest significant rater drift on measures of psychotic symptoms (i.e., total PANSS score). I probed the two-way interaction between raters and time using the recommended procedure for HLMs where this rater drift is graphically depicted (Preacher, Curran, & Bauer, 2003) (Figure 4).

I therefore included this rater by time interaction within the final models utilized for Hypothesis 1, including the four covariates of interest (i.e., IQ, adherence, medication response, age of illness onset), the medication response by study interaction, and the same dependent measures (i.e., PANSS total and subscale scores and BPRS-C total and subscale scores). When rater effects are modeled in the presence of all covariates, the main effect for time on PANSS

total score disappeared (*B*= .83; *p*= .73). The only significant covariates in this final model are the difference between raters 1 and 2 (*B*=27.8; *p*= .03) and the interaction between rater 2 and time (*B*= - 9.89; *p*= .006). These results suggest that during the follow-up period, rater 2 evaluated select psychotic symptoms approximately 9 units lower than the criterion rater for each unit of time (i.e., each study visit). Equivalent results were found for positive and general symptoms as measured by the corresponding PANSS subscales (see Table 5). However, a rater by time interaction was not significant for negative symptoms (*B*= -1.12; *p*= .21) but the main effect for time on negative symptoms was no longer observed in the presence of the rater effect (*B*= -.4; *p*= .53). Results of the final model with and without modeling rater effects can be seen in Tables 4 and 5.

These results suggest that the observed changes in psychotic symptoms as captured by the PANSS total, positive, and general subscales were artifacts of rater bias rather than actual variability in scores. More specifically, rater 2's evaluations of positive and general psychotic symptoms as measured by the PANSS became progressively lower and further from the criterion rater's during the follow-up period. With respect to negative symptoms, a somewhat different pattern emerged. Specifically, a rater by time interaction was not observed when negative symptoms were assessed and the main effect for time was no longer significant with respect to negative symptoms.

Importantly, rater effects were not observed when the BPRS-C is the dependent measure. In the presence of all other covariates, including raters and the rater by time interaction term, a significant main effect for time is still observed such that general psychiatric symptoms as measured by the BPRS-C decreased significantly during the follow-up period (*B*= -5.0; *p*= .000). In addition, the study by medication response interaction also remained significant (*B*= -24.9; *p*= .01). I probed this 2 -way interaction within using recommended procedure for HLMs

(Preacher et al., 2003) (Figure 5). This interaction suggests significant differences in levels of general psychiatric symptoms as measured by the BPRS-C based on initial study membership and medication response within that study. Specifically, youth who were medication responders in TAPS have higher BPRS-C scores than non-responders. In contrast, youth were initially medication responders within TEOSS or ZEOSS have lower levels of overall psychiatric symptoms. Importantly, there are fewer participants and overall observations for youth originally enrolled in TEOSS (n=14) than youth from TAPS (n=24) which limit what may be concluded about these study differences.

To further examine the nature of observed changes in general psychiatric symptoms based on study membership with respect to time, I examined a graph of average BPRS-C total scores during the follow-up period by original study membership (see Figure 6). This depicts the rough trajectory of average general psychiatric symptoms during the follow-up period. Visual inspection of this plot shows that the scores of participants originally enrolled in TAPS (i.e., youth with both affective psychotic disorders and schizophrenia spectrum) appear higher on average (as found in the significant interaction). With respect to the temporal sequence of symptomatic change, the graph suggests that the steepest decline in general psychiatric symptoms occurred early in the follow-up period, between baseline and the first Long Term Course observation.[4]

Conclusions about sensitivity analyses

These additional analyses of rater effects suggest that rater 2's evaluations of positive and general psychotic symptoms drove the main effect for time previously observed within the

[4] Time was coded by number of repeated measures observation/study visit within analyses due to the unbalanced nature of data collection. Specifically, follow-up intervals were highly variable and not uniformly scheduled (i.e., only a few participants had data available at each time point). I therefore aggregated time data by visit number due to the sparseness of data collection. Coding time in this way limits the within subject variability but provides better estimates of between subject variability.

HLMs. Importantly, the observed rater effect was limited to measures of certain psychotic symptoms (i.e., PANSS total, positive and general subscales), as modeling rater effects did not change the main effect of time on levels of general psychiatric symptoms as measured by the BPRS-C. Further, when rater effects are modeled, the interaction between study and medication response continued to predict significant variance in total BPRS-C score such that youth who were medication responders in the TAPS study had higher levels of psychiatric symptoms whereas medication responders in the TEOSS investigation had lower levels of general psychiatric symptoms.

Supplementary Analyses

Given that the course of psychotic symptoms was of primary interest to the current study, I repeated the analyses contained in Hypothesis 1 using a subgroup of youth from the overall sample for whom PANSS data was not affected by rater bias (n= 20). However, when rater 2's data is excluded, only one participant originally enrolled in the TEOSS investigation remained, thus it was impossible to estimate a study effect and evaluate the medication response by study interaction within this model. I therefore examined the predictive effects of the four original covariates (i.e., IQ, age of onset, medication response, medication adherence ratings) on symptom levels during the follow-up period and no interactions as originally modeled within Hypothesis 1.

Results of these supplemental analyses indicate that psychotic symptoms as measured by the total PANSS score and each subscale did not show a main effect for time on symptoms levels (B=1.84; p= .41) and none of the covariates significantly predicted variance in symptom levels during the follow-up period. Thus, excluding the biased ratings of psychotic symptoms eliminated the main effect of time but provided no additional information about the predictive utility of the covariates on levels of symptoms that I initially evaluated.

CHAPTER 4

DISCUSSION

The current study prospectively evaluated the longitudinal effects of four risk factors on psychotic and general psychiatric symptoms among a sample of children and adolescents with early onset psychotic disorders, including schizophrenia spectrum and affective disorders with psychosis. Primary analyses (i.e., HLM) initially indicated a main effect for time such that levels of psychotic and general psychiatric symptoms decreased significantly during the follow-up period. However, none of the hypothesized covariates (i.e., IQ, age of onset, medication adherence ratings, medication response) explained significant variance in the observed changes. Secondary descriptive analyses using regression failed to characterize further the relationship between illness course and the covariates of interest.

The finding that psychotic symptoms decreased significantly during the follow-up period was somewhat unexpected and was not explained by the four covariates of interest. Thus, I evaluated two design-related explanations (i.e., rater and study effects) with a series of sensitivity analyses. Evaluating rater effects suggested that observed changes in all PANSS scores (except the negative symptom subscale) within the original models appeared to be an artifact of rater bias rather than actual variability in symptom scores. The presence of rater effects in the final model did not, however, change the nonsignificant effects of the four original covariates on levels of symptoms. When HLMs were reexamined excluding observations affected by rater bias, symptoms did not decrease over time and none of the covariates predicted variance in the PANSS total score or any subscales. Unfortunately, these re-analyses excluded over half of this

study's observations, further limiting the statistical power to detect effects and not permitting an analysis of interactions.[5]

Examination of study effects suggested a significant interaction between original study membership and medication response on general psychiatric symptoms as measured by the BPRS-C. Indeed, with respect to levels of general psychiatric symptoms, the main effect for time and an interaction between medication response and study were unaffected by rater bias and remained significant. These findings, and my interpretations of them, are discussed below.

First, the covariates I evaluated did not predict significant variance in psychotic symptoms during the follow-up period. Analyses of psychotic symptoms were limited, however, by a number of design and methodological problems. With respect to design characteristics, youth originally enrolled in TAPS lacked baseline PANSS data which limited the range of my analyses for this outcome since these youth comprised the majority of the current sample (n=24). Concerning methodological limitations, biased ratings of select psychotic symptoms compromised over half of the sample's observations. Subsequent analyses which excluded biased observations (n=20) were even more underpowered than the study's already modest original sample and failed to unearth significant findings.

Second, general psychiatric symptoms as measured by the BPRS-C decreased significantly during the follow-up period although none of the covariates I examined accounted for significant variance in these changes. Several design characteristics may help explain this finding. Specifically, baseline BPRS-C data were collected prior to youth receiving antipsychotic medication within the original trials when symptoms levels were correspondingly acute. Thus, the overall decrease in psychiatric symptoms may partially reflect this early, rapid symptom

[5] Specifically, after excluding rater 2's observations there were very few participants from TEOSS (i.e., one of the original medication studies) which prevented evaluation of the medication response by study interaction on psychotic symptoms.

reduction secondary to antipsychotic response and/or regression to the mean. This significant decrease in general psychiatric symptoms is consistent with reductions in BPRS-C total scores among participants in the original TAPS investigation where reductions of 44-67% from baseline BPRS-C scores were observed across treatment groups (Sikich et al., 2004). Visual inspections of average BPRS-C total scores during the follow-up period support this interpretation, with the steepest symptomatic declines occurring between baseline (i.e., pre-medication) and the first follow-up visit in Long Term Course (see Figure 6). Previous research has suggested the importance of evaluating the clinical course of psychotic illness during stabilized states versus acute ones (Maziade et al., 1996), an observation echoed by the current findings.

The observed decrease in psychiatric symptoms during the follow-up period is perhaps most confidently interpreted relative to original medication study membership and medication response given the significance of this interaction within the final models. It is somewhat unexpected that youth with primarily affective psychoses (i.e., those from TAPS study) considered medication responders would have *higher* levels of overall psychiatric symptoms than youth with schizophrenia spectrum illnesses (i.e., those from TEOSS) given that the latter is associated with a more chronic symptomatic course (Eggers et al., 2000; Jarbin et al., 2003; Maziade et al., 1996; McClellan & McCurry, 1999; McClellan et al., 1999). However, this may reflect the unique psychiatric presentation of these diagnostic groups and the sensitivity of the BPRS-C to these phenomena.

Specifically, participants the current study who were initially enrolled in TAPS were more diagnostically varied and included youth affective disorders with psychosis (n=16) and schizophrenia spectrum disorders (n=8). In contrast, youth originally enrolled in TEOSS all had schizophrenia (n=8) or schizoaffective disorder (n=6). Accordingly, the presentation of

psychopathology among youth with psychosis in the context of affective disorders may vary in important ways from youth with a schizophrenia spectrum illness. More specifically, youth with schizophrenia spectrum disorders are distinguished from youth with affective psychosis by a predominance of negative symptoms and greater social withdrawal (McClellan et al., 2003; McClellan et al., 1999), domains to which a global measure of behavioral problems such as the BPRS-C may be less sensitive. In contrast, youth with affective psychoses, notably bipolar disorder, are more likely to present with greater acutely agitation and overt irritability (Pavuluri, Herbener, & Sweeney, 2004). As a measure of behavioral and global psychiatric symptoms (Overall & Pfefferbaum, 1982), the BPRS-C is likely more sensitive to these characteristics than the comparatively subtler presentation of youth with schizophrenia spectrum disorders. A comparison of results of this interaction with the PANSS as a dependent measure would lend support for this interpretation but there is not sufficient data to evaluate this claim further. Thus, due to the aforementioned design limitations including the larger number of participants from one medication study (i.e., TAPS, n=24), conclusions about comparative level of illness on the basis of the BPRS-C ratings alone should be made cautiously.

Thus, the interaction between medication response and study is perhaps most noteworthy for its potential methodological implications for future research with this population. Importantly, medication response did not itself predict variance in levels of symptoms but rather, in the presence of a study effect. There thus appear to be factors embedded within the medication trials (or for which the study effect served as proxy) that influence, in combination with other variables of interest, levels of symptoms over time. A range of design-related factors, including contact with study personnel and hospital staff, active monitoring, may have influenced the current findings. These factors have the potential to limit

the external validity of these kinds of studies but also suggest the importance of modeling study effects within data analyses.

Finally, it is important to discuss the issue of rater bias and its effects on the results. Previous research on rater bias has described its varying sources, including characteristics of raters themselves (i.e., individual differences, theoretical orientation, clinical sophistication, age) as well as features of the phenomenon under investigation (Hill, O'Grady, & Price, 1988). With respect to EOP, the presence of rater bias in the current study underscores the difficulty of assessing psychotic symptoms among children and adolescents even among trained evaluators, and the complexity of positive symptoms in particular. These difficulties are certainly consistent with the high rates of misdiagnosis of psychotic disorders seen within community settings (Calderoni et al., 2001; McKenna et al., 1994) and the challenge of reliably and validly evaluating psychosis in youth (Cepeda, 2007; Semper & McClellan, 2003). The fact that rater bias did not affect negative symptoms may reflect the fact that many negative symptoms (e.g., apathy, impoverished or disorganized speech, increased latency of response) are more observable than positive symptoms and thus easier to rate reliably. Indeed, the particular difficulties associated with evaluating positive symptoms in youth is well described (Cepeda, 2007; Pilowsky, 1986) and is reflected by the more extensive training required to achieve reliability on a measure such as the PANSS (Kay et al., 1987). These factors suggest that biased ratings may be more likely on measures of psychotic symptoms than general psychiatric symptoms.

Strengths and limitations

There are several methodological strengths of the current study when compared to the extant literature. Most notably is its prospective design and use of standardized assessments of symptoms during the follow-up period although rater effects limited their utility within data analysis. The rigorous diagnostic characterization of participants remains a strength, however,

given the commonality of misdiagnosis with this population and the over reliance on retrospectively derived diagnoses in the wider literature.

In addition, extremely few longitudinal studies on EOP have examined predictors of illness course at all and the majority of available studies present results only descriptively or using multiple regression analyses. Thus, the current evaluation of clinically relevant covariates and the application of statistical techniques most appropriate for the analysis of repeated measures data reflect contributions. Indeed, because previous research on the longitudinal course of EOP has been limited to descriptive analyses and/or hierarchical regression which violate important assumptions about repeated measures data, the current application of HLM is considered an important contribution and one on which future investigations should build.

Although the current study's sample size is modest, it is comparable to (Eggers & Bunk, 1997; McClellan & McCurry, 1999; Ropcke & Eggers, 2005) and in cases larger than (Asarnow, 2005; Asarnow & Tompson, 1999; Eggers et al., 2000) published reports on this population. It is nevertheless likely that despite the observed rater effects, the current study's limited sample, modest number of repeated measures, and the heterogeneity associated with the different protocols of the original medication studies limited the detection of effects, should they exist, among the covariates of interest.

An important limitation of the current study is its naturalistic design, and therefore the absence of specific and standardized treatments throughout the observation period. The observational nature of the follow-up period likely introduced sources of unobserved heterogeneity in the sample (i.e., varying levels of treatment, etc.) that created more noise relative to signal within data analyses. Additionally, there were no variables related to family constructs available for analysis which are of particular interest to the developmental model of child psychopathology (Cummings et al., 2000) and EOP in particular (Miklowitz, 2004; Tompson,

Asarnow, Goldstein, & Miklowitz, 1990; Tompson, Asarnow, Hamilton, & Newell, 1997).

A final limitation includes a lack of concomitant functional measures in addition with symptomatic ones, especially given the chronic social and functional impairment associated with schizophrenia across the lifespan (Jarbin et al., 2003; Mueser & McGurk, 2004). It should be noted that the observed decrease in general symptoms over time does not necessarily correlate with clinically meaningful changes in the lives of study participants. Indeed, it is important to consider the extent to which observed changes in symptom levels over time reflect clinically significant change in addition to statistical difference. The lack of functional measures in this study prevents the analysis of relationships among clinical and functional variables which are necessary to clarify the observed changes in symptoms. Extrapolating clinical change from change in symptom measures alone is problematic (Jacobson & Truax, 1991), with research only recently attempting to clarify the clinical significance of percentage change scores among adults with schizophrenia by their comparison to measures designed to capture broader clinical judgment (Leucht & Engel, 2006; Leucht et al., 2006).

In addition, symptom change, while important, if not considered as important an index of meaningful change as measures of social and occupational functioning within the recovery movement among adults with schizophrenia (Bellack, 2006). Symptom measures alone may be particularly limited with respect to children and adolescents for whom additional behavioral measures of relevant contexts such as school, social and family functioning are important complements to symptom measurement (Cicchetti & Rogosch, 2002; Eyberg et al., 1998). An early, seminal review of longitudinal studies of illness course among adults with schizophrenia argued that discrepant findings about illness outcome in adult schizophrenia is attributable to varying definitions of remission across studies (Westermeyer & Harrow, 1988). This has particular relevance for the modest but evolving longitudinal literature among youth with EOP

and the importance of including multidimensional outcomes measures within future longitudinal investigations.

Finally, the current results must be interpreted relative to the issue of sampling and the representativeness of this sample with respect to the larger population of youth with EOP. Although treatment was not standardized during the follow-up period, the majority were considered adherent to prescribed medication based on self-report (i.e., 86%). Although self-report data tends to overestimate adherence (Velligan et al., 2006) it nevertheless indicates, at the very least, most participants' involvement with a prescribing physician. This characteristic alone may distinguish study participants from the broader population of youth with EOP or be a proxy variable for other phenomena (e.g., access to healthcare, help-seeking behaviors). Indeed, the fact that all participants initially participated in medication trials raises the possibility that the current sample constitutes a population that is unique from the broader population of youth with psychotic disorders in important ways.

Examination of participant flow and recruitment within the TAPS (the initial medication trial in which most of the current study's participants were enrolled (n=24)) illustrates this critical issue of representativeness. Specifically, of the 160 children and adolescents assessed for eligibility, 109 were not randomized. As Sikich and colleagues report (2004), reasons included a failure to meet inclusion criteria and geographic distance from the hospital that prevented participation. The vast majority (n=74), however, refused to participate. Although additional data on these refusals are not presented, it is possible that the reasons behind these refusals (e.g., attitudes toward medication and/or medical professionals, discomfort with the randomization process, etc.) reflect potential differences between those ultimately enrolled in TAPS and thus the current study and the larger population of youth with EOP and their families.

Future Directions

This study was limited to a descriptive analysis of several clinically relevant risk factors associated with more severe symptoms. Although none of the covariates I examined predicted significant variance in the observed changes in general psychiatric symptoms, the importance of future research on clinically relevant risk factors remains great, especially with respect to future applied research for affected youth and their families. In order to be most useful with respect to treatment development, additional study is required to determine the *processes* by which these and other fixed and potentially modifiable factors confer such risk. As Cowan and colleagues (1996) have suggested, "The active ingredients of a risk lie not in the variable itself, but in the set of processes that flow from the variable, linking specific conditions with dysfunctional outcomes" (p. 9).

Perhaps the most important future directions this study can recommend, however, are methodological considerations for the continued study of this unique child population. These recommendations encompass three broad domains: the importance of the developmental psychopathology perspective within psychiatric research, related measurement considerations, and the utility of modeling clinician effects.

First, the perspective of developmental psychopathology has important implications for future psychiatric research on youth with EOP although this integration poses significant methodological challenges. Early onset schizophrenia is believed to develop from the complex interplay between genetic susceptibility and environmental risk (Rapoport & Inoff-Germain, 2000) and thus naturally requires methodologies that account for these multiple levels of analysis. However, youth with EOP are most commonly studied in the context of medication trials where primary outcome measures emphasize symptomatic domains. It is recommended that future research distinguish measures sensitive to medication response such as the BPRS-C

(Lachar et al., 2001) and those which more broadly capture the multiple levels of analysis that characterize the developmental psychopathology perspective. Such measures include combined methods of data collection (i.e., questionnaires and observational methods) (Cummings et al., 2000) and the evaluation of contextual factors that inform illness presentation among youth with EOP (e.g., family, peer, sociocultural factors). The continued evaluation of medication for affected youth remains an urgent research priority (Kumra et al., 2008) but the aims and designs of medication trials may differ in important ways from those best suited to answer questions about longitudinal illness course. When possible, such studies should represent distinct investigations to avoid the problems the current study encountered in combining samples from different medication trials. The current results additionally suggest the importance of following youth during non-acute periods of illness (i.e., following medication stabilization) in order to more confidently evaluate psychosocial covariates of interest independent of and in relation to medication effects (Maziade et al., 1996).

Indeed, these theoretical recommendations regarding measurement are empirically bolstered by the adult literature on schizophrenia in which functional and symptomatic domains frequently represent independent phenomena and require distinct measures (Green et al., 2004). Moreover, functional domains are frequently of greater concern to patients themselves than psychotic symptoms per se (Bellack, 2006). Thus, in order to advance the development of adjunctive psychosocial treatments for affected youth as well as to better understand the effects of medication on broader aspects of child functioning, future research must utilize functional measures in addition to symptomatic ones. Moreover, such measures must assess functional outcomes within contextual domains most relevant to child psychopathology (i.e., family related constructs, parenting, peer relationships) given their potentially rich clinical application (Cummings et al., 2000). Indeed, social withdrawal and impaired social functioning are well

described antecedents in the developmental histories of youth with EOP (Eggers & Bunk, 1997; McClellan et al., 2003; Schaeffer & Ross, 2002), domains highly associated with quality of life and functioning among adults with schizophrenia (Roberts, Penn, Cather, Otto, & Goff, 2004). Such findings suggest its importance as a treatment target and warrant the characterization of social functioning in youth with EOP in both cross sectional and longitudinal contexts.

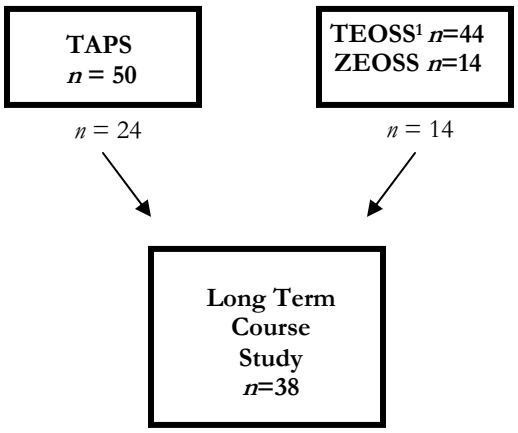
Finally, the discussion of rater effects and their potential to systematically bias data collection has implications for future studies of EOP and clinical research more broadly. The current study underscores the value of routinely evaluating the effects of "human error" within statistical analyses above and beyond interim reliability checks and/or other forms of protocol fidelity. This may be particularly critical when the phenomenon of interest are psychotic symptoms in childhood which are very complex to reliably diagnose in a cross-sectional context (McKenna et al., 1994), let alone to observe over time (Carlson, 1990; Eggers & Bunk, 1997). The statistical modeling of investigator-driven effects can powerfully influence result interpretation and more precisely identify variables driving the observed findings. Indeed, the parallel literature on statistically modeling therapist effects within therapy trials is a distinct but related form of evaluating sources of bias embedded in the researchers themselves as they relate to clinical outcomes (Martindale, 1978; Wampold & Brown, 2005; Wykes et al., 2005). Indeed, a failure to model characteristics of therapists (i.e., level of training, allegiance to the model under investigation) can obscure the most efficacious elements of an intervention (Crits-Cristoph, Tu, & Gallop, 2003; Wykes et al., 2005) much as inattention to rater factors can limit the validity of data capture.

The observed rater by time interaction has additional clinical implications within and beyond a research context. Specifically, this interaction demonstrates the potential pitfall of clinicians overestimating clinical change in the absence of reliably applied standardized outcome

measures as well as behaviorally-defined assessments (e.g., grades, involvement in social activities). Clinician-specific factors, including favorable qualities such as investment in the psychotherapy process and the individual in one's care, may positively bias evaluations of symptoms to the client's detriment by overestimating change. Thus, the current study underscores the importance not only of utilizing standardized assessments to characterize change within a repeated measures context but also statistically modeling unobserved researcher/clinician effects and the application of methods appropriate for the analysis of nested factors (Wampold & Serlin, 2000).

Figure 1

Enrollment of Long Term Course participants from one of three initial medication trials (i.e., TAPS, ZEOSS or TEOSS)



[1]Both TEOSS and ZEOSS were multisite studies. These values reflect UNC's participants and thus the population from which Long Term Course studies were recruited (TEOSS overall *n*=119; ZEOSS overall *n*=40).

Table 1

Demographic and clinical features of 38 Long Term Course participants by diagnosis

	Schizophrenia N=14	Schizoaffective N=7	Bipolar N=7	Major Depression N=10	F/χ^2	*p*
Male n (%)					x^2=14.3	.002*
Age at study enrollment (in years)	14.1±3.3	11.8±3.3	14.0±3.3	12.7±3.0	*F* =1.25	.30
Ethnicity n (%)					x^2=7.31	.60
Caucasian	10 (71%)	4 (57%)	6 (86%)	7 (70%)		
African-American	3 (21%)	2 (29%)	0	2 (20%)		
Hispanic	0	1 (14%)	0	0		
American Indian	1 (7%)	0	1 (14%)	0		
Other	0	0	0	1 (10%)		
Age at onset of first psychotic symptoms (in years)	12.1±3.3	8.8±2.4	13.4±2.8	10.4±3.3	*F* =3.09	.04*
Baseline BPRS-C					*F*=2.08	.12
Total	47.35±8.2	41.57±7.9	53.85±9.9	46.3±10.9		
Behavioral	5.35±3.4	3.28±3.1	4.42±4.1	3.6±2.8		
Mania	5.8±2.7	8.14±3.6	7.57±4.3	6.1±2.7		
Depression	5 ±3.2	4.8±3.2	8.4±4	8.4±3.5		
Thinking disturbance	12.14±3	11±2.9	11±2.5	11.4±2.3		
Baseline PANSS					*F*=5.5	.008*
Total[a]	90.42±31.7	85.75±10.1				
Positive	23.7±9.8	24.8±4.5	---	---		
Negative	24.92±8.5	20.6±4.65				
General	46.28±16.9	45±5.97				
Number of previous diagnoses	1.6 ± 1.8	2.8±1.7	2±1.5	1±1	*F*=1.83	.16
Number of prior hospitalizations	1.64±1.44	1.75±1.83	1.28±1.38	.33±.5	*F*=2.06	.12
IQ	92.6±16.7	85.6±11.2	118.8±18.9	106.7±18.2	*F*=23.55	.000*
Originally enrolled in TAPS (n, %)	6 (43%)	1 (14%)	7 (100%)	10 (100%)		
Originally enrolled in TEOSS (n, %)	8 (57%)	6 (86%)	---	---		

Note. All values presented are *M*±*SD*.
* $p < .05$

[a] Baseline PANSS data are available for youth who initially participated in TEOSS (i.e., youth with schizophrenia spectrum disorders only; *n*=14).

BPRS-C = Brief Psychiatric Rating Scale for Children; subscales=behavioral problems, mania, and depression. PANSS= Positive and Negative Syndrome Scale; subscales=positive symptoms, negative symptoms, and general psychopathology.

Table 2

Baseline characteristics of the Long Term Course sample

Baseline characteristic	Total (n=38)
Mean age at enrollment (years±SD)	13.1±2.8
Mean age of illness onset (years±SD)	11.28±3.36*
Male Gender (*n*, %)	21 (55%)
Primary Diagnoses (*n*, %)	
Schizophrenia	14 (36.8%)
Schizoaffective disorder	7 (18.4%)
Major depression with psychosis	10 (26.3%)
Bipolar disorder with psychosis	7 (18.4%)
Ethnicity (*n*, %)	
White, non-Hispanic	28 (73.7%)
Black, non-Hispanic	7 (18.4%)
Hispanic	1 (2.6%)
American Indian	1 (2.6%)
Other or non-specified	1 (2.6%)
IQ (*M*±*SD*)	95.9±19.2
Number of prior hospitalizations (*M*±*SD*)	1.3±1.4
Repeated a grade in school (*n*, %)	11 (29%)
BPRS-C total (*M*±*SD*)[a]	47.2±9.7
Mania subscale	6.6±3.27
Depression subscale	6.5±3.81
Behavior problems subscale	4.3±3.37
Thinking disturbance	11.5±2.69
PANSS total (*M*±*SD*)[b]	98.7±18.84
Positive symptoms	28.3±5.1
Negative symptoms	24.1±7.5
General scale	50.7±9.8

[a] BPRS-C=Brief Psychiatric Scale for Children (total score for the published sample's mean for youth with psychotic disorders =49, for entire clinical sample=27.8; Lachar et al., 2001)
[b] PANSS=Positive and Negative Symptom Scale (published sample's mean total score=65; Kay et al., 1987). Baseline PANSS data are available for 14 subjects.
* Includes the age of onset outlier. Mean age = 11.66±2.7 when outlier is excluded.

Table 3

Correlation table

	PANSS[a] total	BPRS-C total	age of onset	IQ	medication adherence	medication response
PANSS total	---					
BPRS-C total	0.76*	---				
age of onset	-0.05	-0.04	---			
IQ	-0.06	-0.12	-0.12	---		
medication adherence	-0.00	-0.18*	-0.09	0.19*	---	
medication response	.01	-0.01	0.11	.15#	.05	---

*$p < .05$, #$p < .10$

[a] Correlations involving the PANSS reflect only unbiased ratings (i.e., rater 2's data were excluded).

^This mean includes the age of onset outlier. When this individual is excluded values did not significantly change.

Figure 2

Quantile quantile plots of the primary outcome measures

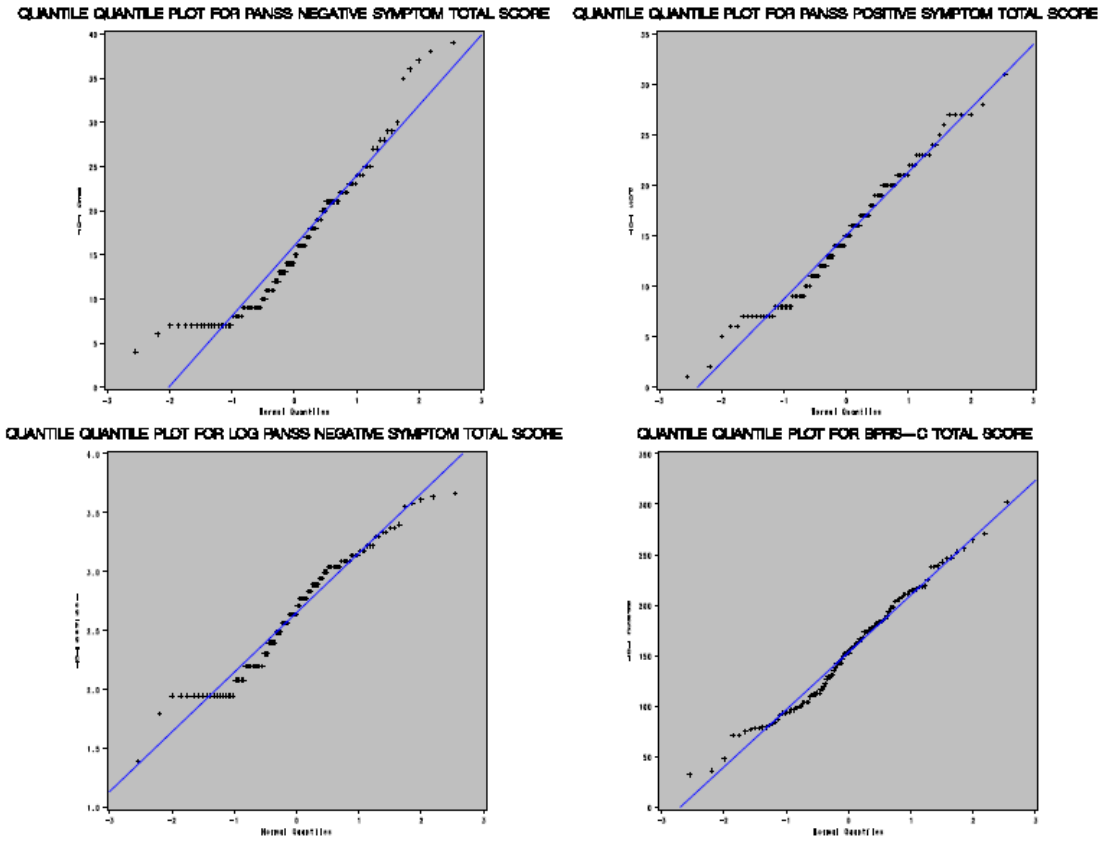


Figure 3

Predicted values plotted against age of onset

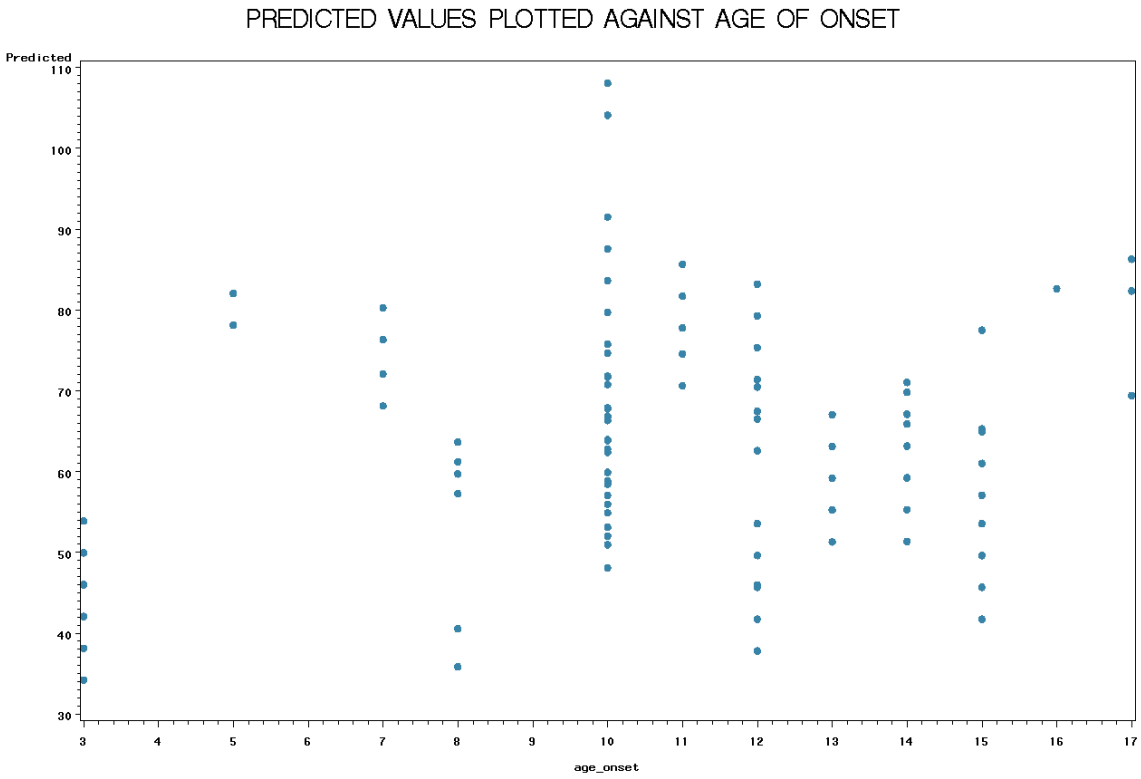


Table 4

Fixed effects in the prediction of psychotic symptoms and when rater effects are not modeled

	Unstandardized betas for outcomes			
Predictors	PANSS total	PANSS positive	PANSS negative	PANSS general
Level 1				
Time	-3.93 **	-1.16 **	-.93 **	-1.91 **
Level 2				
Age of onset	.37	-.04	.22	.23
IQ	.05	.02	-.41	.05
Medication response	-5.68	-1.4	-1.83	-2.3
Medication adherence	-2.95	-3.2	2.92	-2.6
Study	-1.5	1.4	-1.4	-1.5
Medication response*study	-31.7	-10.10#	-7.8	-16.1

PANSS = Positive and Negative Syndrome Scale
* $p < .05$; ** $p \leq .01$, #$p = .05$

Table 5

Fixed effects in the prediction of psychotic symptoms when rater effects are included in the model

	Unstandardized betas for outcomes			
Predictors	PANSS total	PANSS positive	PANSS negative	PANSS general
Level 1				
Time	.83	.54	-.42	.49
Raters 1 and 2	27.8	7.79*	3.4	13.47#
Rater 1 and 2* time	-9.89**	3.13**	-1.12	-5.12**
Level 2				
Age of onset	2.67	.45	.38	.49
IQ	.29	.05	-.02	.07
Medication response	7.5	5.5	-2.14	5.58
Medication adherence	-10.37	-4.4	2.7	-6.11
Study	49.29	7.9	-3.39	.83
Medication response*study	-12.8	-11.12	-9.79	-10.34

PANSS = Positive and Negative Syndrome Scale
* $p < .05$; ** $p \leq .01$, #$p = .05$

Table 6

Fixed effects for the prediction of general psychiatric symptoms

	Unstandardized betas for outcomes			
Predictors	BPRS-C Total	BPRS-C Behavior	BPRS-C Depression	BPRS-C Mania
Level 1				
Time	-4.5**	-.73**	-.72**	-.85**
Level 2				
Age of onset	.29	-.12	.14	-.09
IQ	.01	.008	.01	-.009
Medication response	9.4	2.25	.46	2.7#
Medication adherence	-3.9	-1.71	-.99	-.29
Study	12.76	2.58	-.07	3.5#
Medication response*study	-21.18*	-3.22	-1.14	-3.7#

BPRS-C = Brief Psychiatric Rating Scale for Children
* $p < .05$; ** $p \leq .01$, #$p < .1$

Table 7

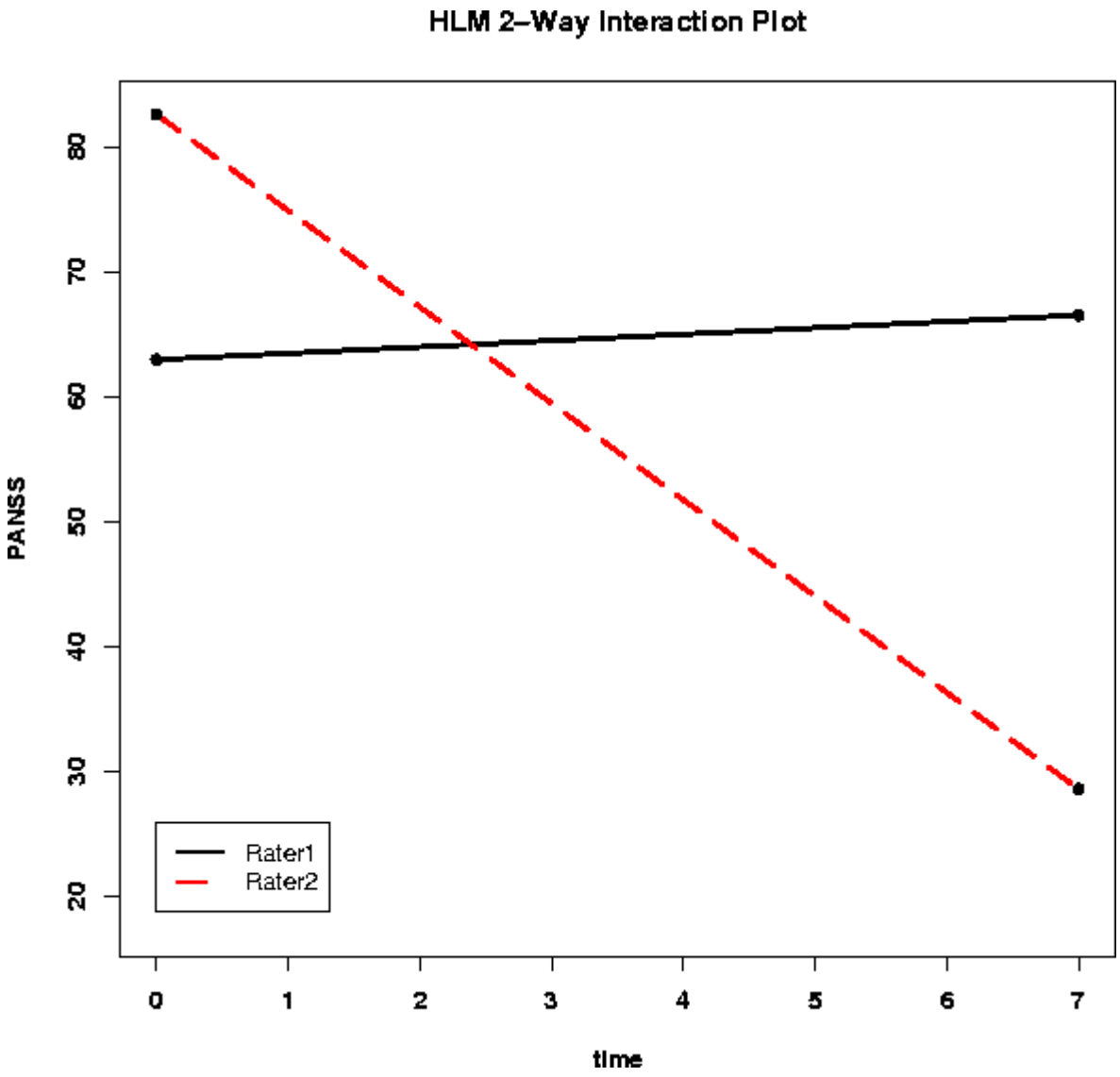
Fixed effects for the prediction of general psychiatric symptoms when rater effects are included in the model

	Unstandardized betas for outcomes			
Predictors	BPRS-C Total	BPRS-C Behavior	BPRS-C Depression	BPRS-C Mania
Level 1				
Time	-5.0**	-.31	-1.34**	-.86**
Rater 1 and rater 2	5.2	-.08	-.55	-.93
Rater 1 and 2*time	-.28	-.46	.79	.12
Level 2				
Age of onset	.54	-.13	.12	-.08
IQ	.05	.001	.01	-.005
Medication response	11.77	1.9	.63	2.7
Medication adherence	-4.3	-1.58	-.87	-.32
Study	11.97	2.7	-.14	4.28
Medication response*study	-24.92**	-2.75	-1.27	- 4.09#

BPRS-C = Brief Psychiatric Rating Scale for Children
* $p < .05$; ** $p \leq .01$, #$p < .1$

Figure 4

Two-way interaction between raters and time on measures of psychotic symptoms



Rater 1= criterion rater
Range of time = baseline (0) to final repeated measure (7)

Figure 5

Two-way interaction between medication response by original study membership in the prediction of general psychiatric symptoms

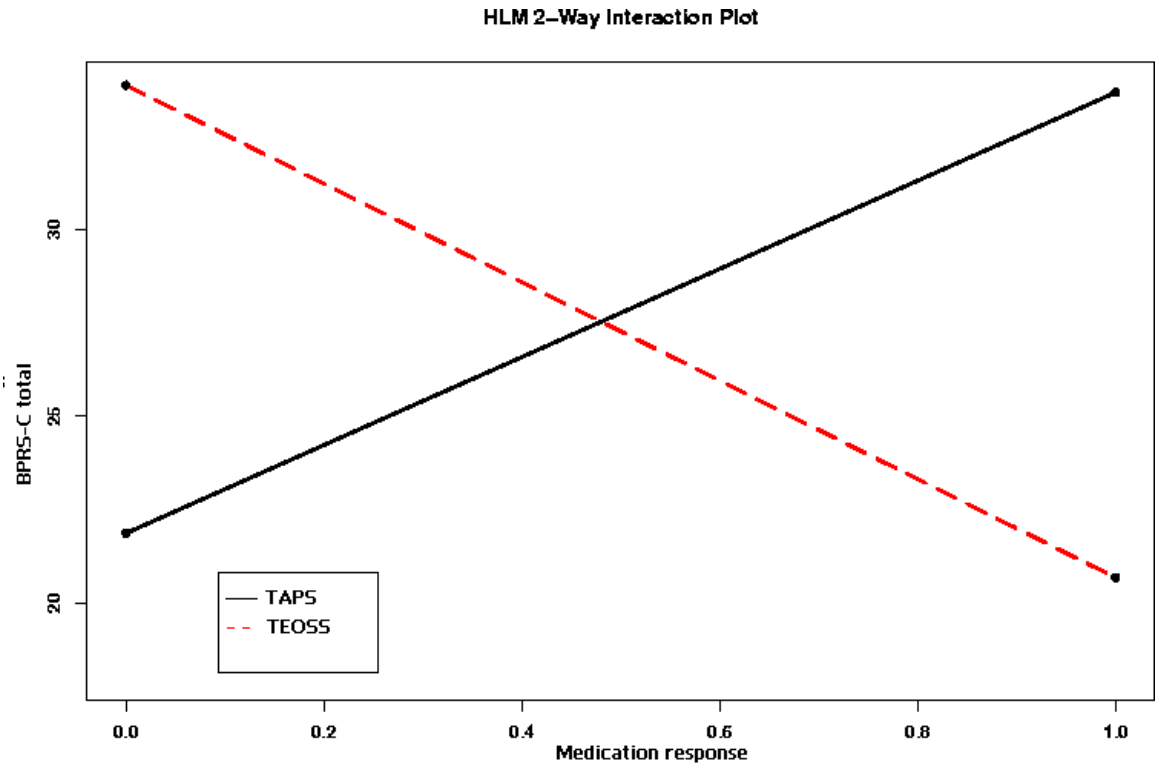
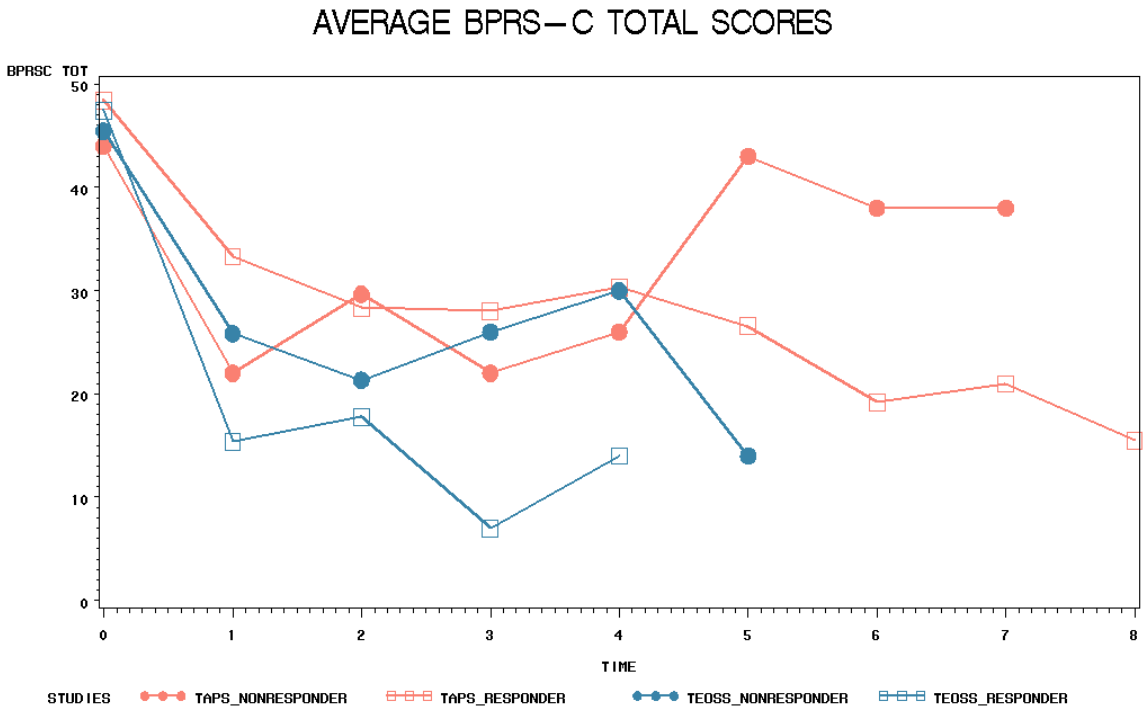


Figure 6.

Average BPRS-C scores during the follow-up period based on original study membership and medication response



REFERENCES

Adams, J., & Scott, J. (2000). Predicting medication adherence in severe mental disorders. *Acta Psychiatrica Scandinavica, 101*(2), 119-124.

Agresti, A. (2002). *Categorical Data Analysis* (Second ed.). New Jersey: Wiley and Sons, Inc.

Alaghband-Rad, J., McKenna, K., Gordon, C. T., Albus, K. E., Hamburger, S., Rumsey, J. M., et al. (1995). Childhood-onset schizophrenia: The severity of premorbid course. *Journal of the American Academy of Child & Adolescent Psychiatry, 34*(10), 1273-1283.

APA. (1994). *Diagnostic and statistical manual of mental disorders (fourth edition)*. Washington D.C.: American Psychiatric Association Press, Inc.

Arango, C., Bombin, I., Gonzalez-Salvador, T., Garcia-Cabeza, I., & Bobes, J. (2006). Randomised clinical trial comparing oral versus depot formulations of zuclopenthixol in patients with schizophrenia and previous violence. *European Psychiatry, 21*(1), 34-40.

Arseneault, L., Cannon, M., Murray, R., Poulton, R., Caspi, A., & Moffitt, T. E. (2003). Childhood origins of violent behaviour in adults with schizophreniform disorder. . *British Journal of Psychiatry, 183*, 520-525.

Asarnow, J. (2005). Childhood-onset schizotypal disorder: a follow-up study and comparison with childhood-onset schizophrenia. *Journal of child and adolescent psychopharmacology, 15*(3), 395-402.

Asarnow, J. R., & Tompson, M. C. (1999). Childhood-onset schizophrenia: A follow-up study. *European Child & Adolescent Psychiatry, 8*(1), 9-12.

Asarnow, J. R., & Tompson, M. C. (1999). Childhood-onset schizophrenia: A follow-up study. *European Child and Adolescent Psychiatry, 8*(Suppl. 1), 1-12.

Asarnow, J. R., Tompson, M. C., & McGrath, E. P. (2004). Annotation: Childhood-onset schizophrenia: clinical and treatment issues. *Journal of Child Psychology and Psychiatry, 45*(2), 180-194.

Asarnow, R. F., Brown, W., & Strandburg, R. (1995). Children with a schizophrenic disorder: Neurobehavioral studies. *European Archives of Psychiatry and Clinical Neuroscience, 245*(2), 70-79.

Bachmann, S., Bottmer, C., & Schroder, J. (2005). Neurological soft signs in first-episode schizophrenia: A follow-up study. *American Journal of Psychiatry, 162*(12), 2337-2343.

Ballageer, T., Malla, A., Manchanda, R., Takhar, J., & Haricharan, R. (2005). Is adolescent-onset first episode psychosis different from adult onset? *Journal of the American Academy of Child & Adolescent Psychiatry, 44*(8), 782-789.

Bauer, D. J., & Curran, P. J. (2006). Multilevel Modeling. Unpublished manuscript.
. University of North Carolina at Chapel Hill.

Bellack, A. S. (2006). Scientific and consumer models of recovery in schizophrenia: concordance, contrasts, and implications. *Schizophrenia Bulletin, 32*, 432-442.

Biederman, J., Petty, C., Faraone, S. V., & Seidman, L. (2004). Phenomenology of childhood psychosis: Findings from a large sample of psychiatrically referred youth. *Journal of Nervous and Mental Disease, 192*(9), 607-614.

Birmaher, B., Axelson, D., Strober, M., Gill, M. K., Valeri, S., Chiappetta, L., et al. (2006). Clinical course of children and adolescents with bipolar spectrum disorders. *Archives of General Psychiatry, 63*, 175-183.

Burd, L., & Kerbeshian, J. (1987). A North Dakota prevalence study of schizophrenia presenting in childhood. *Journal of the American Academy of Child & Adolescent Psychiatry, 26*(3), 347-350.

Caetano, S. C., Olvera, R. L., Hunter, K., Hatch, J. P., Najt, P., Bowden, C., et al. (2006). Association of psychosis with suicidality in pediatric bipolar I, II and bipolar NOS patients. *Journal of Affective Disorders, 91*(1), 33-37.

Calderoni, D., Wudarsky, M., Bhangoo, R., Dell, M. L., Nicolson, R., Hamburger, S. D., et al. (2001). Differentiating childhood-onset schizophrenia from psychotic mood disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*(10), 1190-1196.

Campbell, D. T., & Fiske, D. W. (1959). Convergent and discriminant validations by the multitrait-multimethod matrix. *Psychological Bulletin, 56*, 81-105.

Carlson, G., Bromet, E. J., & Sievers, S. (2000). Phenomenology and outcome of subjects with early and adult-onset psychotic mania. *American Journal of Psychiatry, 157*(2), 213-219.

Carlson, G. A. (1990). Annotation: Child and adolescent mania: Diagnostic considerations. *Journal of Child Psychology and Psychiatry, 31*(3), 331-341.

Carlson, G. A., Bromer, E. J., Driessens, C., Mojtabai, R., & Schwartz, J. E. (2002). Age at onset, childhood psychopathology, and 2-year outcome in psychotic bipolar disorder. *American Journal of Psychiatry, 159*(307-309).

Carlson, G. A., & Kashani, J. H. (1988). Phenomenology of major depression from childhood through adulthood: Analysis of three studies. *American Journal of Psychiatry, 145*(10), 1222-1225.

Castro-Fornieles, J., Parellada, M., Gonzalez-Pinto, A., & al, e. (2007). The child and adolescent first-episode psychosis study (CAFEPS): Design and baseline results. *Schizophrenia Research, 91*, 226-237.

Cather, C., Penn, D. L., Otto, M. W., Yovel, I., Mueser, K. T., & Goff, D. C. (2005). A pilot study of functional cognitive behavioral therapy (fCBT) for schizophrenia. . *Schizophrenia Research, 74*, 201-209.

Cepeda, C. (2007). Differential diagnosis of psychotic disorders: psychiatric disorders associated with psychosis. In C. Cepeda (Ed.), *Psychotic Symptoms in Children and Adolescents: Assessment, Differential Diagnosis, and Treatment* (pp. 153-202). New York: Routledge.

Cepeda, C. (2007). Psychiatric assessment. In *Psychotic symptoms in children and adoelscents: Assessment, differential diagnosis, and treatment.* (pp. 25-49). New York: Routledge

Chambers, W. J. (1985). The assessment of affective disorders in children and adolescents by semistructured interview: Test-retest reliability of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode Version. *Archives of General Psychiatry, 42*(7), 696-702.

Chambers, W. J., Puig-Antich, J., Tabrizi, M. A., & Davies, M. (1982). Psychotic symptoms in prepubertal major depressive disorder. *Archives of General Psychiatry, 39*(8), 921-927.

Cicchetti, D. (2006). *Development and Psychopathology* (Vol. 1). Hoboken, New Jersey: John Wiley & Sons, Inc.

Cicchetti, D., & Rogosch, F. A. (2002). A developmental psychopathology perspective on adolescence. *Journal of Consulting and Clinical Psychology, 70*(1), 6-20.

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

Cowan, P. A., Cowan, P. A., & Schulz, M. S. (1996). Thinking about risk and resilience in families. In E. M. Hetherington & E. Blechman (Eds.), *Risk and resilience: Advances in family research.* (Vol. 5, pp. 1-38). Hillsdale, NJ: Erlbaum.

Crits-Cristoph, P., Tu, X., & Gallop, R. (2003). Therapists as fixed versus random effects-Some statistical and conceptual issues: A comment on Siemer and Joormann. . *Psychological Methods, 8*(4), 518-523.

Cummings, E. M., Davies, P. T., & Campbell, S. B. (2000). What is developmental psychopathology? In E. M. Cummings, P. T. Davies & S. B. Campbell (Eds.), *Developmental Psychopathology and Family Process: Theory, Research, and Clinical Implications* (pp. 17-34). New York: The Guilford Press.

DelBello, M., Hanseman, D., Adler, C., Fleck, D. E., & Strakowski, S. M. (2007). Twelve-month outcome of adolescents with bipolar disorder following hospitalization for a manic or mixed episode. *American Journal of Psychiatry, 154*(4), 582-590.

DeQuardo, J. R., Goldman, R. S., Tandon, R., McGrath-Giroux, M., & Kim, L. (1995). Comparison of indices of premorbid function in schizophrenia. *Schizophrenia Research, 15*(3), 283-290.

Donohoe, G., Owens, N., O'Donnell, C., Burke, T., Moore, L., Tobin, A., et al. (2001). Predictors of compliance with neuroleptic medication among inpatients with schizophrenia: A discriminant function analysis. *European Psychiatry, 16*(5), 293-298.

Dunlop, D. D. (1994). Regression for longitudinal data: A bridge from least squares regression. *The American Statistician, 48*(4), 299-303.

Eggers, C. (1978). Course and prognosis in childhood: A follow-up study. *Journal of autism and developmental disabilities, 19*, 327-334.

Eggers, C., & Bunk, D. (1997). The long-term course of childhood-onset schizophrenia: A 42-year followup. *Schizophrenia Bulletin, 23*(1), 105-117.

Eggers, C., Bunk, D., & Krause, D. (2000). Schizophrenia with onset before the age of eleven: clinical characteristics of onset and course. *Journal of autism and developmental disabilities, 30*(1), 29-38.

Eggers, C., Bunk, D., Volberg, G., & Ropcke, B. (1999). The ESSEN study of childhood-onset schizophrenia: selected results. *European Child and Adolescent Psychiatry, 8*(Suppl 1), 21-28.

Emslie, G. J., Rush, A. J., Weinberg, W. A., Rintelmann, J. W., & Roffwarg, H. P. (1994). Sleep EEF features of adolescents with major depression. *Biological Psychiatry, 36*, 573-581.

Eyberg, S. M., Schuhmann, E. M., & Rey, J. (1998). Child and adolescent psychotherapy research: Developmental issues. *Journal of Abnormal Child Psychology, 26*(1), 71-82.

Farmer, K. C. (1999). Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical Therapeutics: The International Peer-Reviewed Journal of Drug Therapy, 21*(6), 1074-1090.

First, M. C., Gibbon, M., Spitzer, R. L., & Williams, J. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1), Clinician Version*. Washington D.C.: American Psychiatric Association Press, Inc.

Frazier, J. A., McClellan, J., Findling, R. L., Vitiello, B., Anderson, R., Zablotsky, B., et al. (2007). Treatment of early-onset schizophrenia spectrum disorders (TEOSS): demographic and clinical characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(8), 969-978.

Gale, J., Pfefferbaum, B., Suhr, M. A., & Overall, J. E. (1986). The Brief Psychiatric Rating Scale for Children: a reliability study. *Journal of Clinical Child Psychology, 15*(4), 341-345.

Geller, B., Fox, L. W., & Clark, K. A. (1994). Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. *Journal of the American Academy of Child & Adolescent Psychiatry, 33*(4), 461-468.

Geller, B., Tillman, R., Craney, J. L., & Bolhofner, K. (2004). Four year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Archives of General Psychiatry, 61*, 459-467.

Gerralda, M. E. (1984). Hallucinations in children with conduct and emotional disorders: II. The follow-up study. *Psychological Medicine, 14*, 597-604.

Gitlin, M., Nuechterlein, K., Subotnik, K. L., Ventura, J., Mintz, J., Fogelson, D. L., et al. (2001). Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. . *American Journal of Psychiatry, 158*, 1835-1842.

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, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia Research, 72*(1), 41-51.

Green, W., Padron-Gayol, M, Hardesty, AS, Bassiri, M. (1992). Schizophrenia with childhood-onset: A phenomenological study of 38 cases. *journal of the American Academy of Child and Adolescent Psychiatry, 31*(5), 968-976.

Greenwald, D. F., Harder, D. W., Gift, T. E., & Strauss, J. S. (1989). IQ as a prognostic indicator in adult psychiatric first admissions. *Journal of Clinical Psychology 45*(1), 37-50.

Hien, D., Matzner, F. J., Spitzer, R. L., Gibbon, M., & Williams, J. (1998). *Structured Clinical Interview for DSM-IV – Child Edition (Version 1.0).*

Hill, C. E., O'Grady, K. E., & Price, P. (1988). A method for investigating sources of rater bias. *Journal of Counseling Psychology, 35*(3), 346-350.

Hlastala, S. A., & McClellan, J. (2005). Phenomenology and diagnostic stability of youths with atypical psychotic symptoms. *Journal of child and adolescent psychopharmacology, 15*(3), 497-509.

Hollingshead, A. B. (1957). Two-factor index of social position. Yale University.

Hollis, C. (1995). Child and adolescent (juvenile onset) schizophrenia: A case control study of premorbid developmental impairments. *British Journal of Psychiatry, 166*, 489-495.

Hollis, C. (2000). Adult outcomes of child- and adolescent-onset schizophrenia: Diagnostic stability and predictive validity. *American Journal of Psychiatry 157*, 1652-1659.

Jacobsen, L. K., & Rapoport, J. K. (1998). Research update: childhood-onset schizophrenia: implications of clinical and neurobiological research. *Journal of Child Psychology and Psychiatry, 39*(1), 101-113.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 59*(1), 12-19.

Jarbin, H., Ott, Y., & von Knorring, A.-L. (2003). Adult outcome of social function in adolescent-onset schizophrenia and affective psychosis. *Journal of the American Academy of Child & Adolescent Psychiatry, 42*(2), 176-183.

Jarbin, H., & VonKnorring, A. (2004). Suicide and suicide attempts in adolescent-onset psychotic disorders. *Nordic Journal of Psychiatry, 58*, 115-121.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. . *Schizophrenia Bulletin, 13*, 262-276.

Kay, S. R., Opler, L. A., & Fiszbein, A. (1986). Significance of positive and negative syndromes in chronic schizophrenia. *British Journal of Psychiatry, 149*, 439-448.

Kazdin, A. E., & Kendall, P. C. (1998). Current progress and future plans for developing effective treatments: Comments and perspectives. *Journal of Clinical Child Psychology, 27*(2), 217-226.

Kemph, J. P., Braley, R. O., & Ciotola , P. V. (1998). A comparison of youthful inmates who have committed violent versus nonviolent crimes. *Journal of the American Academy of Psychiatry and the Law, 26*(1), 67-74.

Kumra, S., Jacobsen, L. K., Lenane, M., & al., e. (1998). "Multidimensionally impaired disorder." Is it a variant of very early-onset schizophrenia? *Journal of the American Academy of Child & Adolescent Psychiatry, 37*, 91-99.

Kumra, S., Oberstar, J. V., Sikich, L., Findling, R. L., McClellan, J. M., Vinogradov, S., et al. (2008). Efficacy and tolerability of the second-generation antipsychotics in children and adolescents with schizophrenia. *Schizophrenia Bulletin, 34*(1), 60-71.

Kumra, S., Wiggs, E., Bedwell, J., Smith, A. K., Arling, E., Albus, K., et al. (2000). Neuropsychological deficits in pediatric patients with childhood-onset schizophrenia and psychotic disorder not otherwise specified. *Schizophrenia Research, 42*(2), 135-144.

La Greca, A. M., & Schuman, W. B. (1995). Adherence to prescribed medical regimens. In M. C. Roberts (Ed.), *Handbook of pediatric psychology* (second ed.). New York: Guilford press.

Lachar, D., Randle, S., Harper, A., Scott-Gurnell, K. C., Lewis, K. R., Santos, C. W., et al. (2001). The Brief Psychiatric Rating Scale for Children (BPRS-C): validity and reliability of an anchored version. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*(3), 333-340.

Leucht, S., & Engel, R. R. (2006). The relative sensitivity of the clinical global impressions scale and the brief psychiatric rating scale in antipsychotic drug trials. *Neuropsychopharmacology, 31*, 406-412.

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.

Little, R. J. A., & Rubin, D. B. (1987). *Statistical Analysis with Missing Data*. New York: Wiley.

Loranger, A. W. (1984). Sex difference in age at onset of schizophrenia. *Archives of General Psychiatry, 41*(2), 157-161.

Martindale, C. (1978). The therapist-as-fixed-effect fallacy in psychotherapy research. *Journal of Consulting and Clinical Psychology, 46*, 1526-1530.

Maziade, M., Bouchard, S., Gingras, N., & al., e. (1996). Long-term stability of diagnosis and symptom dimensions in a systematic sample of patients with onset of schizophrenia in childhood and early adolescence. II: positive/negative distinction and childhood predictors of adult outcome. *British Journal of Psychiatry, 169*, 371-378.

McClellan, J., Breiger, D., McCurry, C., & Hlastala, S. (2003). Premorbid functioning in early-onset psychotic disorders. *Journal of the American Academy of Child and Adolescent Psychiatrt, 42*(6), 666-672.

McClellan, J., & McCurry, C. (1999). Early onset psychotic disorders: Diagnostic stability and clinical characteristics. *European Child and Adolescent Psychiatry, 9*(Suppl. 1), 1-19.

McClellan, J., McCurry, C., Snell, J., & DuBose, A. (1999). Early-onset psychotic disorders: course and outcome over a 2-year period. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(11), 1380-1390.

McClellan, J., McCurry, C., Speltz, M., & Jones, K. (2002). Symptom factors in early-onset psychotic disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 41*(7), 791-798.

McClellan, J., Prezbindowski, A., Breiger, D., & McCurry, C. (2004). Neuropsychological functioning in early onset psychotic disorders. *Schizophrenia Research, 68*(1), 21-26.

McClellan, J., Sikich, L., Findling, R. L., Frazier, J. A., Vitiello, B., Hlastala, S. A., et al. (2007). Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS): Rationale, Design, and Methods. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(8), 969-978.

McClellan, J., Werry, J., Bernet, W., Arnold, V., Beitchman, J., Benson, S., et al. (2001). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*, 4S-23s.

McClellan, J. M., Werry, J. S., & Ham, M. (1993). A follow-up study of early onset psychosis: Comparison between outcome diagnoses of schizophrenia, mood disorders, and personality disorders. *Journal of Autism and Developmental Disorders, 23*(2), 243-262.

McKenna, K., Gordon, C. T., Lenane, M. C., & Kaysen, D. e. a. (1994). Looking for childhood-onset schizophrenia: The first 71 cases screened. *Journal of the American Academy of Child & Adolescent Psychiatry, 35*(5), 636-644.

McShane, G., M., M., G., W., & Rey, J. (2006). Outcome of patients with unipolar, bipolar, and psychotic disorders admitted to a specialist child and adolescent mental health service. *Australian Psychiatry 14*(2), 198-201.

Merry, S. N., & Werry, J. S. (2001). Course and prognosis. In H. Remschmidt (Ed.), *Schizophrenia in children and adolescents.* (pp. 268-297). Cambridge: Cambridge University Press.

Miklowitz, D. J. (2004). The role of family systems in severe and recurrent psychiatric disorders: A developmental psychopathology view. *Development and Psychopathology, 16*(3), 667-688.

Miklowitz, D. J., & Hooley, J. M. (1998). Developing family psychoeducational treatments for patients with bipolar and other severe psychiatric disorders: A pathway from basic research to clinical trials. *Journal of Marital & Family Therapy, 24*(4), 419-435.

Mueser, K. T., & McGurk, S. R. (2004). Schizophrenia. *The Lancet, 363*, 2063-2072.

National Advisory Mental Health Council's Workgroup on Child and Adolescent Mental Health Intervention, D. a. D. (2001). Blueprint for Change: Research on Child and Adolescent Mental Health. [Electronic Version]. *NIH Publication 01-4985*. Retrieved December 14, 2005 from http:www.nimh.nih.gov/child/blueprint.cfm.

Nicolson, R., Lenane, M., & Brookner, F. e. a. (2001). Children and adolescents with psychotic disorder not otherwise specified: a 2- to 8-year follow-up study. *Comprehensive Psychiatry, 42*(4), 319-325.

Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports, 10*, 799-812.

Overall, J. E., & Pfefferbaum, B. (1982). The Brief Psychiatric Rating Scale for Children. *Psychopharmacology Bulletin, 18*(2), 10-16.

Overall, J. E., & Pfefferbaum, B. P. (1982). The Brief Psychiatric Scale for Children. *Psychopharmacology Bulletin, 18*, 10-16.

Pavuluri, M. N., Birmaher, B., & Naylor, M. W. (2005). Pediatric Bipolar Disorder: A Review of the Past 10 Years. *Journal of the American Academy of Child & Adolescent Psychiatry, 44*(9), 846-871.

Pavuluri, M. N., Herbener, E. S., & Sweeney, J. A. (2004). Psychotic symptoms in pediatric bipolar disorder. *Journal of Affective Disorders, 80*, 19-28.

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

Pfefferbaum, B., Mullins, D., Rhoades, H. M., & McLaughlin, E. J. (1987). Rorschach assessment of borderline children. *Journal of Psychology, 121*, 219-228.

Pilowsky, D. (1986). Problems in determining the presence of hallucinations in children. In D. Pilowsky & W. Chambers (Eds.), *Hallucinations in children.* Washington D.C.: American Psychiatric Press.

Preacher, K. J., Curran, P. J., & Bauer, D. J. (2003). Simple intercepts, simple slopes, and regions of signficance in HLM 2-way interactions., from http:///www.psych.ku.edu/preacher/interact/hlm2.htm

Putnam, F. W., Hornstein, N., & Peterson, G. (1996). Clinical Phenomenology of Child and Adolescent Dissociative Disorders: Gender and Age Effects. *Child and Adolescent Psychiatric Clinics of North America, 5*(2), 351-360.

Rapoport, J. L., & Inoff-Germain, G. (2000). Update on childhood-onset schizophrenia. *Current Psychiatry Reports, 2*, 410-415.

Raudenbush, S. W. (2002). *Hierarchical linear models: applications and data analysis methods* (Second ed.). Thousand Oaks: Sage Publications.

Reimherr, J. P., & McClellan, J. M. (2004). Diagnostic Challenges in Children and Adolescents With Psychotic Disorders. *Journal of Clinical Psychiatry, 65*, 5-11.

Remschmidt, H., Martin, M., Fleischhaker, C., Theisen, F. M., Hennighausen, K., Gutenbrunner, C., et al. (2007). Forty-two years later: the outcome of childhood-onset schizophrenia. *Journal of Neural Transmission, 114*, 502-512.

Remschmidt, H., Martin, M., Schulz, E., Gutenbrunner, C., & Fleischhaker, C. (1991). The concept of positive and negative schizophrenia in child and adolescent psychiatry. In A. Marneros, N. O. Andreasen & M. T. Tsuang (Eds.), *Negative Versus Positive Schizophrenia* (pp. 219-242). New York: Springer-Verlag.

Roberts, D. L., Penn, D. L., Cather, C., Otto, M., & Goff, D. C. (2004). Should CBT Target the Social Impairments Associated With Schizophrenia? *Journal of Cognitive Psychotherapy, 18*(3), 255-264.

Robinson, D. G., Woerner, M. G., Alvir, J. M. J., Bilder, R., Goldman, R., Geisler, S., et al. (1999). Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry, 56*, 241-247.

Ropcke, B., & Eggers, C. (2005). Early-onset schizophrenia: a 15-year follow-up. *European Child and Adolescent Psychiatry, 14*, 341-350.

Ross, R. G., Heinlein, S., & Tregellas, H. (2006). High rates of comorbidity are found in childhood-onset schizophrenia. *Schizophrenia Research, 88*(1), 90-95.

Ryan, N. D., Puig-Antich, J., Ambrosini, P., & Rabinovich, H. (1987). The clinical picture of major depression in children and adolescents. *Archives of General Psychiatry, 44*(10), 854-861.

Sax, K. W., Strakowski, S. M., Keck, P. E., McElroy, A. L., West, S. A., Bourne, M. L., et al. (1997). Comparison of patients with early-, typical- and late-onset affective psychosis. *American Journal of Psychiatry, 154*(9), 1299-1301.

Schaeffer, J. L., & Ross, R. G. (2002). Childhood-onset schizophrenia: Premorbid and prodromal diagnostic and treatment histories. *Journal of the American Academy of Child & Adolescent Psychiatry, 41*(5), 538-545.

Schaeffer, J. L., & Ross, R. G. (2002). Childhood-onset schizophrenia: Premorbid and prodromal diagnostic and treatment histories. *Journal of American Academy of Child and Adolescent Psychiatry, 41*(5), 538-545.

Schwartz, J. E., Fennig, S., Tanenberg-Karant, M., Carlson, G., Craig, T., Galambos, N., et al. (2000). Congruence of diagnosis 2 years after a first-admission diagnosis of psychosis. *Archives of General Psychiatry, 57*(6), 593-600.

Semper, T. F., & McClellan, J. M. (2003). The psychotic child. *Child and Adolescent Psychiatric Clinics of North America, 12*, 679-691.

Shirk, S. R. (1999). Development and the search for prescriptive child treatments. In D. Cicchetti & S. L. Toth (Eds.), *Rochester Symposium on Developmental Psychopathology: Developmental Approaches to Prevention and Intervention* (Vol. 9, pp. 311-340). Rochester: University of Rochester Press.

Sibitz, I., Katschnig, H., Goessler, R., Unger, A., & Amering, M. (2005). Pharmacophilia and Pharmacophobia: Determinants of Patients' Attitudes towards Antipsychotic Medication. *Pharmacopsychiatry, 38*(3), 107-112.

Sikich, L., Hamer, R. M., Bashford, R. A., Sheitman, B. B., & Lieberman, J. A. (2004). A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology, 19*, 133-145.

Srinath, S., Janardhan, R. Y. C., Girimaji, S. R., & Seshadri, S. P. (1997). Diagnostic stability of psychoses of childhood and adoscent onset. *NIMHANS Journal, 15*(2), 199-127.

Sroufe, L. A. (1997). Psychopathology as an outcome of development. *Development and Psychopathology, 9*(2), 251-268.

Sroufe, L. A., & Rutter, M. (1984). The domains of developmental psychopathology. *Child Development, 55*, 17-29.

Stayer, C., Sporn, A., Gogtay, N., Tossell, J. W., Lenane, M., Gochman, P., et al. (2005). Multidimensionally Impaired: The Good News. *Journal of Child and Adolescent Psychopharmacology, 15*(3), 510-519.

Stayer, C., Sporn, A., & Gogtay, N. e. a. (2005). Multidimensionally impaired: the good news. *Journal of child and adolescent psychopharmacology, 15*(3), 510-519.

Strober, M., & Carlson, G. (1982). Bipolar illness in adolescents with major depression: Clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. *Archives of General Psychiatry, 39*(5), 549-555.

Tolbert, H. A. (1996). Psychoses in children and adolescents: A review. *Journal of Clinical Psychiatry, 57*(3), 4-8.

Tompson, M. C., Asarnow, J. R., Goldstein, M. J., & Miklowitz, D. J. (1990). Thought disorder and communication problems in children with schizophrenia spectrum and depressive disorders and their parents. *Journal of Clinical Child Psychology, 19*(2), 159-168.

Tompson, M. C., Asarnow, J. R., Hamilton, E. B., & Newell, L. E. (1997). Children with schizophrenia-spectrum disorders: Thought disorder and communication problems in a family interactional context. *Journal of Child Psychology and Psychiatry, 38*(4), 421-429.

Turkington, D., Kingdon, D., & Weiden, P. (2006). Cognitive behavior therapy for schizophrenia. *American Journal of Psychiatry, 163*, 365-373.

Ulloa, R. E., Birmaher, B., Axelson, D., Williamson, D. E., Brent, D. A., Ryan, N. D., et al. (2000). Psychosis in a pediatric mood and anxiety disorders clinic: Phenomenology and correlates. *Journal of the American Academy of Child & Adolescent Psychiatry, 39*(3), 337-345.

Varanka, T. M., Weller, R. A., Weller, E. B., & Fristad, M. A. (1988). Lithium treatment of manic episodes with psychotic features in prepubertal children. *American Journal of Psychiatry, 145*(12), 1557-1559.

Velligan, D. I., Lam, Y.-W. F., Glahn, D. C., Barrett, J. A., Maples, N. J., Ereshefsky, L., et al. (2006). Defining and Assessing Adherence to Oral Antipsychotics: A Review of the Literature. *Schizophrenia Bulletin, 32*(4), 724-742.

Volkmar, F. R. (1996). Childhood and adolescent psychosis: A review of the past 10 years. *Journal of the American Academy of Child & Adolescent Psychiatry, 35*(7), 843-851.

Walker, E. (1991). Research on life-span development in schizophrenia. In E. Walker (Ed.), *Schizophrenia: A life-course developmental perspective* (pp. 1-6). New York: Academic Press, Inc.

Wampold, B. E., & Brown, G. S. (2005). Estimating variability in outcomes attributable to therapists: A naturalistic study of outcomes in managed care. *Journal of Consulting and Clinical Psychology, 73*(5), 914-923.

Wampold, B. E., & Serlin, R. C. (2000). The consequences of ignoring a nested factor on measures of effect size in analysis of variance. *Psychological Methods, 5*(4), 425-423.

Watt, N., Anthony, E. J., Wynne, L., & Rolf, J. E. (1984). *Children at risk for schizophrenia: A longitudinal perspective*. New York: Cambridge University Press.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Psychological Corporation.

Weisz, J. R., & Hawley, K. M. (2002). Developmental factors in the treatment on adolescents. *Journal of Consulting and Clinical Psychology, 70*(1), 21-43.

Weisz, J. R., & Weersing, V. R. (1999). Psychotherapy with children and adolescents: efficacy, effectiveness, and developmental concerns. In D. Cicchetti & S. L. Toth (Eds.), *Rochester Symposium on Developmental Psychopathology: Developmental Approaches to Prevention and Intervention* (Vol. 9, pp. 341-380). Rochester: University of Rochester Press.

Werry, J. S., & McClellan, J. M. (1992). Predicting Outcome in child and adolescent (early onset) schizophrenia and bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatrt, 31*(1), 147-150.

Werry, J. S., McClellan, J. M., Andrews, L. K., & Ham, M. (1994). Clinical features and outcome of child and adolescent schizophrenia. *Schizophrenia Bulletin, 20*(4), 619-630.

Werry, J. S., McClellan, J. M., & Chard, L. (1991). Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: A clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(3), 457-465.

Weschler, D. (1981). *Manual for the Weschler Adult Intelligence Scale—Revised*. San Antonio: The Psychological Corporation.

Weschler, D. (1991). *Manual for the Wechsler Intelligence Scale for Children. (3rd ed.)* San Antonio: The Psychological Corporation.

Westermeyer, J. F., & Harrow, M. (1988). Course and outcome in schizophrenia. In M. T. Tsuang & J. C. Simpson (Eds.), *Nosology, Epidemiology and Genetics of Schizophrenia* (Vol. 3, pp. 205-244). New York: Elsevier.

White, T., Ho, B., Ward, J., O'Leary, D., & Andreasen, N. O. (2006). Neuropsychological performance in first episode adolescents with schizophrenia: A comparison with first episode adults and adolescent control subjects. *Biological Psychiatry, 60*, 463-471.

Wozniak, J. R., White, T., & Schulz, S. C. (2005). Neuropsychological Factors in Early-Onset Schizophrenia. In R. L. Findling & S. C. Schulz (Eds.), *Juvenile-Onset Schizophrenia: Assessment, Neurobiology, and Treatment* (pp. 125-147). Baltimore: The Johns Hopkins University Press.

Wykes, T., Hayward, P., Thomas, N., Green, N., Surguladze, S., Fannon, D., et al. (2005). What are the effects of group cognitive behaviour therapy for voices? A randomised control trial. *Schizophrenia Research, 77*, 201-210.

Yang, P., Liu, C. Y., Chiang, S. Q., & Chen, J. Y. e. a. (1995). Comparison of adult manifestations of schizophrenia with onset before or after 15 years. *Acta Psychiatrica Scandinavica, 91*(3), 209-212.