FACULTY OF HEALTH AND MEDICAL SCIENCES
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PhD Thesis

Marie Stentebjerg-Olesen, MD

The phenomenology of early-onset Schizophrenia and related psychoses

- and the early treatment response to antipsychotic medication

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Supervisors

Principal supervisor: Associate professor Pia Jeppesen, Child and Adolescent Mental Health Center, Mental Health Services, Capital region of Denmark; and Faculty of Health Science, University of Copenhagen.

Project supervisor: Associate professor Anne Katrine Pagsberg, Child and Adolescent Mental Health Center, Mental Health Services, Capital region of Denmark; and Faculty of Health Science, University of Copenhagen.

Additional supervisors:

Professor Chistoph U. Correll, Hofstra North Shore LIJ School of Medicine and the Zucker Hillside Hospital, Department of Psychiatry, 75-59 263rd Street, Glen Oaks, NY 11004, USA

Professor Anders Fink-Jensen, Department of Neuroscience and Pharmacology, Psychiatric Centre Copenhagen, University Hospital Copenhagen and Laboratory of Neuropsychiatry, University of Copenhagen, Denmark

Assessment Committee

Professor Birthe Yding Glenthøj, Center for Neuropsychiatric Schizophrenia Research (CNSR), Copenhagen University Hospital, Psychiatric Center Glostrup, Copenhagen, Denmark

Professor Ingrid Melle, Department of Mental Health and Addiction, Institute of Clinical Medicine, University of Oslo, NORMENT KG Jepsen Centre for Psychosis Research, Building 49, Oslo Univeristy Hospital, Ullevål PO Box 4956 Nydalen, 0424 Oslo, Norway

Professor Martin Lambert, Psychosis Centre, Department of Psychiatry and Psychotherapy, Centre of Psychosocial Medicine, University Medical Center Hamburg-Eppendorf, Martinistreet 52, 20246 Hamburg, Germany

Contents

1. PREFACE

The current PhD study investigates the phenomenology and outcomes of early-onset schizophrenia spectrum psychosis (non-affective psychosis) in children and adolescents with a particular focus on whether the early treatment response to antipsychotic medication may predict clinical significant effects in children and adolescents with psychosis – as described in adults. The PhD-study process began with the recruitment, assessment, and monitoring of patients in the TEA (Tolerability and Efficacy of Antipsychotics in children and adolescents with psychosis) trial in the years 2010-2012. My plan was to use the TEA-data to investigate, if the early response after 2-4 weeks predicted clinically significant effects after 12 weeks of antipsychotic medication. In order to obtain a sufficient number of patients, and thereby a sufficient study power, the TEA-trial extended the inclusion period until the beginning of 2014.

As a consequence of the extension of the recruitment period, the TEA-data have not yet been available for the analyses of the early response as predictor of a clinically significant response. These analyses await the primary, blinded analyses of treatment effects in the randomised design. Instead, I was given the opportunity to study the same research question in two other clinical cohorts, for which the relevant data were already collected.

The current thesis is a synopsis based on three articles. The first paper is a systematic review on the phenomenology and outcomes of non-affective psychosis in children and adolescents. The second and third paper investigate the predictive values of the early antipsychotic response with regard to later clinical response or nonresponse of a given antipsychotic medication using data from two different clinical studies in youth suffering from non-affective psychotic disorders and treated with antipsychotics. One study includes children and adolescents with schizophrenia spectrum psychosis, who were treated naturalistically with antipsychotics in New York, USA, under the leadership of Professor Correll. The other dataset included adolescents with schizophrenia randomized to antipsychotic treatment with olanzapine or placebo at multiple sites in the USA and Russia.

2. SUMMARY IN ENGLISH

Background

The current PhD thesis reviews the phenomenology and outcome of early onset schizophrenia spectrum psychosis, and analyses the predictive validity of an early response (ER) to treatment with antipsychotic (AP) medication for later clinical response, called ultimate response (UR). Early-onset schizophrenia (EOS) spectrum disorders are severe and disabling and seem phenomenological continuous with adult-onset schizophrenia (AOS), except for possibly worse outcomes. Currently, much hope is placed on early identification and early treatment as important means to reduce suffering and improve long-term outcomes. AP medication is recommended, but carries an increased risk of side effects in youths compared with adults, and optimization of treatment is important. Patterns of the early antipsychotic treatment response are an attractive tool to guide clinicians in decisions regarding treatment continuation or abortion. ER and early nonresponse (ENR) have shown to be stable predictors of UR/ultimate nonresponse (UNR) and remission in adults with schizophrenia spectrum psychosis. However, investigations of the early response in children and adolescents are lacking.

Methods

Three thematically linked studies were conducted. The first study is a systematic review based on prospective and cross-sectional studies reporting on the phenomenology and outcome of EOS. In addition to descriptive analyses, exploratory analyses assessed associations between relevant clinical variables. Further, the thesis includes two prospective longitudinal, clinical cohort studies of EOS patients initiated in an AP treatment. Patterns of early response were investigated to determine the predictive value of ER/ENR to predict UR/UNR and remission at study end-point. One study was naturalistic and included 79 youth patients, aged 6-19 years, with schizophrenia spectrum disorder. The majority of the patients were naïve to AP before initiation of one of five different second-generation AP medications (SGAs). ER was defined as a score of "at least minimally improved" on the Clinical Global Impression Improvement (CGI-I) scale, and investigated as predictor of clinical outcome and treatment response, including UR, defined as "much" or "very much improved" on the CGI-I, after 12 weeks. The other study was a post-hoc analysis of a multisite randomized controlled trial (RCT) of olanzapine versus placebo and included 69 adolescent patients, aged 13-17 years, most being non-naïve to AP, randomly allocated to the olanzepine treatment arm. The optimal threshold and timing for ER measurement by the Brief

Psychiatric Rating Scale for Children (BPRS-C) was investigated with regard to the prediction of the UR after 6 weeks of AP treatment. Additionally, well-established prognostic factors were assessed as potential moderators of the association between the ER and the UR.

Results

Results are reported in three scientific papers. The first paper summarizes the phenomenology and outcome of EOS across 35 studies, covering 28 independent samples, including a total of 1506 participants. Youth with EOS were functionally impaired and had moderate to severe levels of positive and negative symptoms and disorganization. During a mean follow-up time of 2.2 years, global function and symptom scale scores improved significantly. A longer duration of untreated psychosis (DUP) was significantly associated with less improvement in functioning over time. Four studies compared DUP in EOS and AOS patients directly and found that EOS patients had a longer mean DUP compared to adult onset patients.

The papers II and III, both exploring ER as a predictor of UR in youth patients treated with AP medication, demonstrated that the majority of symptomatic improvement was already achieved after 2-4 weeks of treatment, and that ER/ENR significantly predicted UR/UNR and remission. Thus, results from adult studies were replicated and extended to youth patients with EOS. The ER measured at 3 weeks using an ER threshold of at least 20% BPRS-C reduction had the best predictive power for UR. Using the CGI-I score of at least "minimally improved" to define the ER (paper II) resulted in predictive values comparable to the ER defined by a 20% BPRS-C reduction (paper III). In both studies, the ER remained a robust and significant predictor of UR, even after adjustment for other predictors of ER/ENR or UR/UNR like age, gender, a diagnosis of schizophrenia, AP naïvity, and extrapyramidal symptoms.

Discussion

Phenomenology, clinical outcome and treatment response in patients with EOS spectrum psychosis are characterized in a systematic review and analyses of two prospective longitudinal studies of EOS. The reviewed data on psychopathology were limited and heterogeneous with regard to the use of definitions, time-points and psychometric instruments. ER was a robust indicator of a later clinically significant treatment response, as well as of remission and functional outcome. CGI-I assessments appear to be clinically useful means of identifying ER, allowing for a time efficient assessment of ER/ENR patterns with significant predictive value for UR and other clinically meaningful outcomes. More prospective studies on the phenomenology in this patient group are needed, as are further investigation of early response patterns in youth with EOS spectrum disorders

to enable determination of the best indicator and time points to either continue a given antipsychotic medication or to switch to another agent. A more individualised psychopharmacological treatment guided by the ER/ENR paradigm may help to reduce the duration of insufficiently treated psychosis, and hence improve the outcome of illness.

3. RESUMÉ PÅ DANSK

Baggrund

PhD afhandlingen beskriver fænomenologien og prognosen ved tidligt debuterende skizofrenispektrum psykoser og analyserer den prædiktive værdi af et tidligt respons (early response, ER) på behandling med antipsykotika (AP) som prædiktor for et senere klinisk respons, kaldet ultimativt respons (UR). Tidligt debuterende skizofrenispektrum tilstande (early onset schizophrenia, EOS) er alvorlige og invaliderende og fremstår fænomenologisk i kontinuum med skizofreni med debut i voksenalderen (adult onset schizophrenia, AOS), fraset en muligt dårligere prognose. Aktuelt er der store forhåbninger til at tidlig identifikation og behandling kan mindske patienternes lidelse og forbedre langtidsprognosen. AP anbefales til børn og unge med psykose, men behandling af denne gruppe patienter indebærer en relativt øget risiko for bivirkninger sammenlignet med voksne, hvorfor det er vigtigt, at behandlingen til denne patientgruppe optimeres. Et tidligt indsættende behandlings-respons på AP kan vise sig at være et vigtigt redskab til at vejlede klinikere i beslutningen om, hvorvidt en given AP-behandling skal fortsættes eller afsluttes. ER og tidligt non-respons (early nonresponse, ENR) har vist sig at være stabile prædiktorer af UR, ultimativt non-respons (ultimate nonresponse, UNR) og remission hos voksne med skizofrenispektrum psykoser, mens der mangler undersøgelser af det tidlige respons hos børn og unge.

Metode

Afhandlingen inkluderer tre tematisk forbundne studier. Det første studie er et systematisk oversigtsstudie baseret på prospektive longitudinelle studier samt tværsnitsstudier omhandlende fænomenologi og prognose ved EOS. Foruden deskriptive analyser, præsenteres eksplorative analyser af associationerne mellem relevante kliniske karakteristika. Derudover inkluderer afhandlingen to prospektive longitudinelle kohortestudier af EOS patienter, der er påbegyndt behandling med et AP. Mønstrene for tidligt indsættende respons på AP blev undersøgt med henblik på at beskrive den prædiktive værdi af ER/ENR for UR/UNR og remission ved forsøgenes

afslutning. Det ene studie var naturalistisk og inkluderede 79 patienter i alderen 6-19 år, med skizofrenispektrum lidelser. De fleste af patienterne var AP-naive før påbegyndelse af ét af fem anden-generations antipsykotika (second-generation antipsychotics, SGA). ER blev defineret som en rating på mindst "minimally improved" på Clinical Global Impression Improvement (CGI-I) skalaen og undersøgt som prædiktor for klinisk prognose og behandlingsrespons, herunder UR, der blev defineret som en rating på "much" eller "very much improved" på CGI-I skalaen efter 12 uger. Det andet studie var et multicenter, randomiseret, placebokontrolleret studie (RCT) af olanzepin versus placebo. Vi inkluderede 69 unge i alderen 13-17 år, hvoraf de fleste havde fået AP tidligere. Kun unge allokeret til behandling med olanzapin blev inkluderet. Vi undersøgte det optimale cutoff og den optimale timing for måling af ER med Brief Psychiatric Rating Scale for Children (BPRS-C) skalaen i forhold til prædiktion af UR efter seks ugers AP behandling. Derudover blev veletablerede prognostiske faktorer undersøgt som potentielle moderatorer af associationen mellem ER og UR.

Resultater

Resultaterne er rapporteret i tre videnskabelige artikler. Den første artikel opsummerer fænomenologi og prognose ved EOS fra 35 studier omfattende 28 kohorter med i alt 1506 deltagere. Børn og unge med EOS havde en dårlig global funktion, samt moderate til svære positive og negative symptomer og disorganisering. I løbet af en gennemsnitlig opfølgningsperiode på 2,2 år forbedredes deres globale funktion og symptomer signifikant. En længere varighed af ubehandlet psykose (duration of untreated psychosis, DUP) var signifikant associeret med mindre forbedring i global funktion over tid. Fire studier sammenlignede DUP hos EOS og AOS patienter direkte, og fandt at patienter med debut i barne- og ungealderen havde en gennemsnitlig længere DUP i forhold til patienter med debut i voksenalder.

I artikel II og III, der begge undersøgte ER som prædiktor for UR hos børn og unge i behandling med AP rettet mod psykose, viste det sig, at hovedparten af den symptomatiske bedring fandt sted i de første 2-4 uger af behandlingen, og at ER/ENR signifikant prædikterede UR/UNR og remission. Resultater fra voksenstudier blev således repliceret og udvidet til at omfatte patienter med EOS. ER målt efter 3 ugers behandling og med et cutoff på mindst 20% reduktion i BPRS-C viste den bedste prædiktive værdi for UR. Anvendelse af en CGI-I rating på mindst "minimally improved" til definition af ER (artikel II) gav prædiktive værdier, der var sammenlignelige med ER defineret som mindst 20% reduktion i BPRS-C score. I begge studier viste ER sig at være en stabil og signifikant

prædiktor for UR, selv efter justering for andre prædiktorer af ER/ENR og UR/UNR såsom alder, køn, skizofrenidiagnose, tidligere AP behandling og ekstrapyramidale symptomer.

Diskussion

Fænomenologi, klinisk forløb og behandlingsrespons hos patienter med tidligt indsættende skizofrenispektrum psykoser er beskrevet i et systematisk oversigtsstudie og ved analyser af to forskellige prospektive, longitudinelle studier af EOS. Oversigtsstudiets data omhandlende psykopatologi var begrænsede og heterogene i forhold til definitioner, måletidspunkter og anvendte psykometriske instrumenter. ER var en robust indikator på et senere klinisk signifikant behandlingsrespons, remission og et bedre sygdomsudfald hvad angår funktion. CGI-I målinger synes at være klinisk brugbare til identifikation af ER. CGI-I giver mulighed for tidseffektivt at måle mønstre for ER/ENR med hensyn til prædiktiv værdi for UR og andre klinisk betydningsfulde effekter. Der er behov for flere prospektive studier, der beskriver fænomenologien hos denne patientgruppe. Der er også behov for flere undersøgelser af mønstre for det tidlige respons hos børn og unge med EOS, for dermed at gøre det muligt at identificere den bedste indikator og de bedste måletidspunkter for beslutningen om enten at fortsætte en given AP behandling eller skifte til et andet præparat. En mere individualiseret psykofarmakologisk behandling, vejledt af ER/ENR paradigmet, kan medvirke til at reducere varigheden af en utilstrækkeligt behandlet psykose, og dermed bedre sygdomsprognosen.

4. LIST OF ARTICLES

Paper I. Stentebjerg-Olesen M, Pagsberg AK, Fink-Jensen A, Correll CU & Jeppesen P. Phenomenology and outcomes of non-affective psychosis in children and adolescents: results from a systematic review and exploratory analysis of correlates – under review Journal of Child and Adolescent Psychopharmacology.

Paper II. Stentebjerg-Olesen M, Jeppesen P, Pagsberg AK, Fink-Jensen A, Kapoor S, Chekuri R, Carbon M, Al-Jadiri A, Kishimoto T, Kane JM, Correll CU. Early-non-response determined by the clinical global impressions scale predicts poorer outcomes in youth with schizophrenia-spectrum disorders naturalistically treated with second-generation antipsychotics. Journal Child Adolesc Psychopharmacol 2013;23:665-675

Paper III. Stentebjerg-Olesen M, Ganocy SJ, Findling RL, Chang K, DelBello MP, Kane JM, Tohen M, Jeppesen P, Correll CU. Early response or nonresponse at week 2 and week 3 predict ultimate response or nonresponse in adolescents with schizophrenia treated with olanzapine: results from a 6-week randomized, placebo-controlled trial – under review European Child and Adolescent Psychiatry

5. ABBREVIATIONS

ADHD attention deficit hyperactivity disorder

AIMS Abnormal Involuntary Movement Scale

AOP adult onset psychosis

AOS adult onset schizophrenia

AP antipsychotic

AUC area under the curve

BARS Barnes Akathisia Scale

BPRS Brief Psychiatric Rating Scale

CGI Clinical Global Impression Scale

COS childhood onset schizophrenia

DSM Diagnostic and Statistical Manual of Mental disorders

DUP duration of untreated psychosis

EOP early-onset psychosis

EOS early-onset schizophrenia

ENR early non-response

EPS extrapyramidal symptoms

ER early response

FE first episode

FGA first-generation antipsychotic

GAF Global Assessment of Functioning

ICD International Classification of Diseases

LOCF last observation carried forward

MD movement disorders

n number of patients

N number of studies

NPV negative predictive value

OCD obsessive-compulsive disorder

ODD oppositional defiant disorder

PANSS Positive And Negative Syndrome Scale

PPV positive predictive value

Psychosis-NOS psychosis-not otherwise specified

RCT randomized clinical trials

ROC curve Receiver Operating Characteristic curve

SAS Simpson-Angus Scale

SGA second-generation antipsychotic

TD tardive dyskinesia

UR ultimate response

UNR ultimate non-response

VEOS very early-onset schizophrenia

6. INTRODUCTION

6.1. Early-onset Schizophrenia Spectrum psychoses

6.1.1. Epidemiology

Up to one third of patients with psychotic illness have an onset of the disorder in childhood or adolescence (Schulz 1998, Young 2004, Amminger 2006, Kumra 2011, Pedersen 2014). Childhood-onset psychotic disorders before the age of 13 years are rare, but there is a considerable increase in prevalence of psychosis during adolescence (Pedersen 2014, Remschmidt 1994, Vyas 2011). Adolescence is a period of time with profound changes in the brain structures and functioning with a complex interplay between biological, psychological and social factors. Many mental health problems and mental health disorders emerge in those years (Werry 1992, Vyas 2012).

Schizophrenia with onset before 18 years of age is called early-onset schizophrenia (EOS), and a sub-group with onset before age 13 is referred to as very-early-onset schizophrenia (VEOS), childhood onset schizophrenia (COS) or "prepubertal" schizophrenia (Masi 2006, Werry 1992, Driver 2013).

According to epidemiological data (1965-2002), the median (10% - 90% percentile) incidence of schizophrenia is estimated 15.2 (7.7-43.0) per 100.000 person years, and the median (10% - 90% percentile) lifetime morbid risk of schizophrenia is 7.2 (3.1-27.1) per 1.000 individuals. The male:female ratio is 1.4:1 (van Os 2009, McGrath 2008). Rates vary three-fold depending on which definition of schizophrenia that is used, a narrow definition according to diagnostic criteria or a broader definition with less specific criteria (van Os 2009), and the incidence shows prominent variation between sites (McGrath 2008). Thus the incidence is higher in urban settings, in developed nations compared with developing nations, and in migrant groups (McGrath 2008).

In Denmark 2000-2012 the lifetime risk of schizophrenia and related disorders, based on population-based health registers data, was 3.78% for males and 3.67% for females (Pedersen 2014). Cumulative incidence rates of schizophrenia spectrum disorders up to 50 years of age were 3.06% for males and 2.43% for females. Both sexes had almost identical incidence rates and cumulative incidences for schizophrenia during childhood and adolescence. From 20 to 50 years of age, males had higher incidence rates and cumulative indices.

Of all schizophrenic disorders, 0.1-1 percent manifest themselves before age 10 (Remschmidt 1994, Kennedy 2007). In a Danish register-based study, the age-standardized incidence rate of EOS in Denmark in the time period 1971-2010 was 3.17 per 100.000 person years in the age group 0-18 years, and 9.10 per 100.000 person years in the age group 12-18 years (Okkels 2013). In the early period from 1971 to 1993 the mean incidence rate of EOS was 1.80 per 100.000 person years, in the age group 0-18 years, whereas the mean incidence rate in the later period from 1994 to 2010 was 5.15 per 100.000 person years, thus considerably higher than in the earlier time period. In the period from 1971 to 1993 Okkels et al found that males in the age group 0-18 years had a significantly higher incidence rate of EOS than females, whereas an equal gender distribution was found in the later period 1994-2010.

Textbooks and reviews generally describe EOS, as characterised by a preponderance of males, an insidious onset (especially in VEOS), a higher frequency of premorbid neurodevelopmental abnormalities, more cytogenic abnormalities, and a stronger biological disposition. Moreover EOS patients are generally thought to have a poorer prognosis due to a more severe and early disruption of brain development. Psychopathologically, EOS patients are, compared to AOS, characterised by less complex or elaborated delusions, hallucinations on several perceptual modalities (but mostly auditive), and more severe negative symptoms, disorganisation, and formal thought disorders (Asarnow 1994, Werry 1992, Masi 2006, Remschmidt 1994, Remschmidt 2012, Usiskin 1999, Kumra 2011, Driver 2013).

6.1.2. Phenomenology (symptom dimensions, factor structure)

Psychosis is defined as a severe disruption of thought and behavior resulting in impairment of reality testing abilities. Psychosis is part of the clinical phenomenology in a range of disorders from organic psychosis, to psychosis in affective disorders and schizophrenia. The diagnosis of psychosis is based on overt changes in a person´s behaviour and functioning with evidence of disrupted thinking (McClellan 2013).

Schizophrenia is characterized by symptoms that can be clustered into the following main dimensions (van Os 2009, Andreasen 1995, Schultz 1999, Flaum 1995):

I. The positive dimension, that can be subdivided into a “psychotic group” comprising delusions and hallucinations, and a “disorganized group” comprising formal thought disorders, and disorganized behaviour

II. The negative dimension encompassing alterations in drive and volition (lack of motivation, reduction in spontaneous speech and social withdrawal).

III. The cognitive symptom dimension, including alterations in neurocognition (difficulties in memory, attention and executive functioning) and

IV. The affective dysregulation, encompassing depressive and manic symptoms

The pattern of co-occurrence of symptoms in schizophrenia patients has been informed by factor analysis studies, that have revealed a three-factor solution for characterising these patterns: the "psychotic" (or "positive") factor comprising delusions and hallucinations, a "negative" factor comprising affective blunting, poverty of speech, avolition and anhedonia and a "disorganized" factor comprising disorganized speech and behaviour and inappropriate affect (Flaum 1995, Andreasen 1995).

Children and adolescents with schizophrenia have been characterized as having a broad based cognitive impairment of on average 1 SD below the norm across a range of cognitive abilities (attention, speed of processing, working and long-term memory, executive function, social cognition). This pattern of generalized cognitive deficits is similar to that identified in adults with schizophrenia, and similar cognitive impairments have been reported in relatives of patients with schizophrenia. The decline in full scale IQ seen in EOS does not seem to reflect deterioration but rather an inability to acquire new information and skills (Kumra 2011, Jepsen 2010). The cognitive impairment show little relation to the psychotic symptoms, it is not much influenced by medication, and shows no improvement despite complete resolution of psychotic symptoms (van Os 2009).

The formal thought disorders, disorganization and negative symptom dimension is often associated with neurocognitive deficits, primarily demonstrated in AOS studies (O´Leary 2000, Dibben 2009, Nieuwenstein 2001), and to some degree in EOS (Banachewski 2000, Jepsen 2010, Brickman 2004) whereas the hallucinations, the delusions, and the affective symptom dimension are less so (van Os 2009, Jepsen 2013).

6.1.3. Evidence for a neurodevelopmental disorder (developmental risk factors)

Schizophrenia is currently understood as a neurodevelopmental disorder with a substantial hereditary component. Family-, twin and adoption studies support a strong genetic component for schizophrenia. A history of schizophrenia in first-degree relatives has been established as the

strongest single indicator of risk of schizophrenia and psychotic disorder (Mortensen 1999). The lifetime risk of developing the illness is 5 to 20 times higher in first-degree relatives of affected probands compared with the general population, and the concordance between monozygotic twins is approximately 40% to 60%. Concordance rates in dizygotic twins and siblings are 5%-15% (McClellan 2013). Vulnerability for schizophrenia is thought to be partly genetic and partly the result of gene-environment interaction.

It has been hypothesized that childhood onset schizophrenia (COS) may represent a population with more genetic and familial load than AOS, which suggests the population of EOS patients as especially adequate to search for risk and etiological factors for the disease (Kumra 2011, Driver 2013).

The neurodevelopmental etiologic model or hypothesis of schizophrenia proposes that adult mental illness has its origins in early developmental disturbance of the nervous system. Central to the hypothesis is the identification of developmental deficits that precede overt clinical symptoms of schizophrenia (Owen 2011, Cannon 2002). One version of the neurodevelopmental model focuses on schizophrenia as a static lesion occurring during foetal brain development, whereas others argue that schizophrenia occurs as a result of a second “hit” in the form of abnormal brain development during adolescence with excessive synaptic and/or dendritic elimination resulting in aberrant neuronal connectivity (Driver 2013).

Birth cohort studies have identified subtle developmental lags and problems from infancy through childhood and adolescence into adulthood in many individuals who develop schizophrenia, suggesting that early developmental deviations may contribute to the pathology underlying the development of psychosis many years later in adolescence and adulthood (Welham 2009, Cannon 2002).

Birth cohort studies also uniformly showed that individuals who develop AOS (or schizoaffective disorder or psychotic symptoms) as a group achieved lower scores on intelligence tests than their peers (Welham 2009). It has been unclear if the cognitive deficit is best characterized as stable or declining. Studies have, however, shown that the cognitive impairments in early-onset psychosis (EOP) are already present at the first episode (FE) of psychosis and show a deteriorating course before but not after the onset of syndromal psychosis (Fagerlund 2006, Bombin 2013, Frangou 2013, Bora 2014, Aas 2014). These results support the neurodevelopmental hypothesis, and emphasize the cognitive developmental impairments as predecessors of psychotic symptoms.

It is now generally understood that COS is a multifactorial illness, characterised by multiple genetic elements each contributing a modest degree of risk and interacting with the environment (Driver 2013).

6.1.3.1. Premorbid developmental impairments

Premorbid developmental impairments are common in EOS and involve almost all domains including the development of motor and speech, as well as social and cognitive abilities. This "pan-dysmaturation" may be evident form the first months of life (Masi 2006, Welham 2009, Remschmidt 2012). The common occurrence of premorbid abnormalities and developmental delays argue for a more severe and early disruption of brain development in EOS (especially VEOS) compared to AOS (Masi 2006).

In the National Institute of Mental Health (NIMH) cohort study of COS pt., 55% of the children had premorbid academic impairments, 72% had premorbid social/behavioural impairments, 51% had premorbid language impairments and 44% had premorbid motor impairments (Driver 2013).

It has been speculated if specific premorbid impairments might be linked to the later development of either a schizophrenia spectrum or affective psychosis (Arango 2014). A birth-cohort study from New Zealand (Cannon 2002) found, that early neuromotor, receptive language and cognitive developmental impairments showed specificity to schizophreniform disorder, whereas emotional problems and interpersonal difficulties were noted in children who later fulfilled the diagnostic criteria for schizophreniform disorder or mania or anxiety/depression. The results suggested some specificity of early motor and attentional or executive impairment to future schizophrenia-related outcomes (Cannon 2006). Paya et al. (Paya 2013) found that EOS patients had more social impairment than patients with early onset bipolar disorder, whereas intellectual premorbid abnormalities were less specific and probably stronger linked to the early onset of the psychosis, and Rietschel et al. (Rietschel 2009) found even better premorbid adjustment in bipolar patients compared to healthy controls. Arango et al. concluded that, at least in early onset cases, neurodevelopmental trajectories seem to be different between schizophrenia and bipolar cases at a quantitative rather than qualitative level (Arango 2014).

6.1.4. Clinical diagnosis (criteria and differential diagnoses)

The diagnostic group termed "Schizophrenia spectrum and other psychotic disorders" include the following disorders (according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic categories): Schizotypal Disorder, Delusional Disorder, Brief Psychotic

Disorder, Schizophreniform Disorder, Schizophrenia, Schizoaffective disorder, Substance/ Medication-Induced Psychotic Disorder, and a few other psychotic disorders presenting either with other disorders or as unspecified disorders.

At the beginning of the 19th century Kraepelin (1913) distinguished between two kinds of endogenous psychosis, dementia praecox and manic-depressive psychoses. The term "schizophrenia" was introduced by Eugen Bleuler (1911) who spoke of the "group of schizophrenias", i.e. different forms of schizophrenia. Leo Kanner (1943) and Hans Asperger (1944) delineated early infantile autism and autistic personality disorder out of the pool of schizophrenic psychoses, and Kolvin (1971) also clearly differentiated schizophrenia from the pervasive developmental disorders (Remschmidt 1994, Masi 2006).

Since the appearance of DSM-III and the International classification of diseases – 9th edition (ICD-9), the diagnostic criteria for schizophrenia have been identical for early-onset and adult onset of the illness, and psychotic disorders in children and adolescents are still diagnosed by the same criteria as for adults according to the current DSM-5 and ICD-10 criteria. The diagnosis of the full syndrome of a schizophrenia-spectrum psychosis shows high diagnostic stability from childhood throughout adolescence and adulthood (Masi 2006, Remschmidt 2012).

There are several important organic and psychiatric diagnoses to rule out before deciding on a schizophrenia diagnosis (McClellan 2013, Driver 2013). Several drugs of abuse and medical conditions (ex. central nervous system infections, neoplasms, endocrine disorders, genetic syndromes) can present themselves with psychosis. Important psychiatric differential diagnoses are affective psychosis (especially bipolar disorder), pervasive developmental disorders, obsessive-compulsive disorder (OCD), generalized anxiety disorder, post-traumatic stress disorder (PTSD) and atypical reports of psychotic symptoms or "multidimensionally impaired" (not a formal DSM diagnosis (McClellan 2013, Driver 2013). Some children and adolescents report symptoms suggestive of hallucinations and delusions but with no overt evidence of psychosis, and particularly youths diagnosed with PTSD, conduct problems or depression have been found to report higher rates of psychotic-like symptoms than controls (McClellan 2013).

Some children with complex neurodevelopmental disorders may show patterns of symptoms across the boundaries of autism spectrum disorders and schizophrenia spectrum disorders. These children typically have brief, transient psychotic symptoms and elements of the classical autistic syndrome (the triad of impairments, Wing 1997) combined with significant disturbances in several domains of functioning, including affect regulation (emotional lability), social behaviour and interaction, and

thought processes. Two constructs have emerged to study and describe those children: The multidimensionally impaired syndrome and multiple complex developmental disorder (MCDD) (Werry 1992, Masi 2006, Cochran 2013, Driver 2013, Buitelaar 1998). However these diagnoses are not included in the most common diagnostic classification systems (currently DSM-5 and ICD-10) but may be categorized according to psychosis-not otherwise specified (NOS). In some of these children the psychotic symptoms seem to improve over time and long-term antipsychotic medication may not be needed (Asarnow 2004, Kennedy 2007, Driver 2013).

6.1.5. Comorbidity (all psychopathology)

COS is highly correlated with other psychiatric illnesses and disorders in childhood and adolescence. The most important comorbidities are obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), anxiety disorder, expressive language disorders, receptive language disorders, and mood disorders, primarily major depressive disorder (Driver 2013, Ross 2006).

A total of 99% of COS patients in a study by Ross et al. had at least one lifetime comorbid axis 1 disorder (according to DSM-IV diagnostic criteria). The most common co-morbid disorder in their sample was ADHD (84%), followed by ODD (43%), depression (30%) and separation anxiety disorder (25%) whereas a history of trauma was rare in this cohort (Ross 2006).

6.1.6. Course and prognosis

Schizophrenia exhibits substantial heterogeneity with respect to severity and course over time. Most patients improve significantly after their FE is treated, but the majority experience subsequent episodes with only a small fraction being able to regain premorbid levels of functionality (Andreasen 2005, Robinson 2004, van Os 2009).

Early onset psychosis/schizophrenia is generally thought to have a poor response to antipsychotic treatment and a poor outcome in terms of educational achievement, likelihood of employment, global disability, and a poverty of social relationships (Remschmidt 2012, Fleischhacker 2005, Kumra 2011, Vyas 2012, Clemmensen 2012). More recently, studies however suggest that with current treatments offered to a broad spectrum of psychotic illnesses in youths, the poor prognosis reported in older studies may not be inevitable (Asarnow 1994, Amminger 2011, Schimmelmann 2007, Rabinowitz 2014).

6.1.7. Treatment recommendations

Treatment of (early onset) psychosis involves both pharmacological and non-pharmacological treatment. Antipsychotic medication that blocks dopamine D2 receptors is the core pharmacological treatment. Non-pharmacological treatment includes psychotherapeutic, psychoeducational, behavioural, social, scholastic and familial intervention (McClellan 2013, Masi 2006, Vyas 2012, Kendall 2013).

6.1.8. The early intervention in psychosis paradigm

In recent years, there has been a focus on early detection of psychosis. The idea is to reduce the delay in effective treatment and thereby improve treatment outcome and long-term prognosis (Masi 2006, Marshall 2005).

Individuals, who develop psychosis, most often experience a prodromal phase with some degree of functional deterioration before the onset of psychotic symptoms. This phase involves changes in perception, behavior, cognition, mood and physiology that may be associated with anxiety, aggressive behaviors or conduct problems, including substance abuse, which might confuse the diagnostic picture (Vyas 2012, Yung 1996, McClellan 2013). The prodromal phase may vary from an acute marked change to a chronic insidious deterioration. There is a non-specificity of symptoms in the prodromal phase, and a low predictive power in the identification of individuals who undergo a transition to psychosis (Vyas 2012, Correll 2010). Hence, there are concerns that over-diagnosing psychosis and diagnosing of early pre-psychotic states of the disorder may result in unnecessary anxiety, antipsychotic treatment, misclassification and stigmatisation.

Early intervention in schizophrenia has two elements, early detection and phase-specific treatment (including psychological, social or physical treatment developed specifically for use with people at an early stage of the illness or in the prodromal phase in order to improve long-term outcome) (Marshall 2011). A Cochrane review on early intervention for psychosis concluded, that there is emerging, but as yet inconclusive, evidence to suggest that people in the prodrome of psychosis can be helped by some interventions. Thus there is some support for specialized early intervention services and treatment focused on employment and family therapy but this needs to be replicated in longer and larger trials (Marshall 2011).

6.1.8.1. Secondary prevention by reduction of duration of untreated psychosis

The duration of untreated psychosis (DUP) is defined as the time from the onset of psychosis to the initiation of adequate treatment.

Longer DUP is associated with a poorer early-course and long-term outcome, and thus DUP is a target for intervention efforts. In an early detection study from Norway and Denmark (Melle 2008) reduction of DUP was related to a better course of symptoms and functioning over a two-year follow-up period. DUP is strongly related to negative symptoms (Boonstra 2012), and the literature suggests that longer duration of untreated illness may reduce the treatment responsiveness of negative symptoms, and efforts to shorten DUP might decrease negative symptom severity and lead to a better outcome (Melle 2008).

Predictors and determinants of DUP was the focus of a study of FE psychosis (Broussard 2013). In this study mode of onset, prior incarceration and the level of childhood/adolescent maltreatment were significant independent predictors of a longer DUP. Having ever used cannabis and the amount of premorbid alcohol use were also significantly associated with longer DUP. Thus, intervention services might focus on young people likely to have a history of maltreatment, alcohol and/or cannabis use, crime, and those with more gradually developing psychosis.

DUP is reported to be longer in children and adolescents than in adults. This may be explained by a number of factors including insidious onset, premorbid abnormalities, pubertal problems, comorbid conditions and reluctance by health professionals to set a diagnosis of psychosis (Schimmelmann 2013, Masi 2006). Hence, it might be even more important to focus on reduction of the DUP in youth than in adult patients.

6.2. Pharmacological treatment of EOS

6.2.1. The efficacy of antipsychotics for treatment of psychosis in children and adolescents

In adults, antipsychotics have proven to be more effective than placebo in improving psychotic symptoms and preventing relapse (Leucht 2009a, Leucht 2012). In the TEA study protocol we have summarized the current evidence-base for use of antipsychotic medication in children and adolescents with psychosis (Pagsberg 2014): The literature includes only six randomised placebo-controlled trials of SGAs in adolescents with schizophrenia (Findling 2008, Kryzhanovskaya 2009, Haas 2009, Singh 2011, Findling 2012, Findling 2013), one randomised placebo-controlled trial of a first-generation (or typical) antipsychotic (FGA) in children with schizophrenia (Spencer 1992),

and 12 randomised clinical trials (RCTs) comparing benefits and harms of different antipsychotic drugs in broader defined EOP patients. Six out of seven placebo-controlled trials showed superiority of the antipsychotic compared with placebo, while one trial was terminated due to lack of efficacy. Five of the 12 RCTs were open-label (van Bruggen 2003, Jensen 2008, Arango 2009, Swadi 2010, Mozes 2006), and seven were double-blinded, head-to-head trials (Kumra 1996, Kumra 2008, Shaw 2006, Sikich 2004, Sikich 2008, clinicaltrials.gov 2013, Realmuto 1984). Across these RCTs, only clozapine has shown superiority compared with other antipsychotics, when used for treatment-resistant EOS (Kumra 1996, Kumra 2008, Shaw 2006). The RCTs included only small to medium size patient samples and thus the use of antipsychotics in EOP is still to a large extent based on extrapolations from trials conducted in adults.

The few available data on efficacy and safety of antipsychotic medication in children and adolescents, and the severity of some adverse effects in adults have raised concerns about the benefit/risk ratio of the use of antipsychotics in youth (Vitiello 2009, Correll 2008, Mattai 2010). SGAs are the mainstay of therapy in children and adolescents (Kumra 2013, McClellan 2013, Kendall 2013, Pagsberg 2014b). Major differences exist in type and severity of adverse effects, and for that reason the choice of antipsychotic medication is primarily guided by tolerability and safety considerations. FGAs improve psychotic symptomatology, but they elicit significant extrapyramidal symptoms (EPS), tardive dyskinesia (TD) and prolactin elevations. SGAs less often elicit EPS and TD but they have significant endocrine and metabolic side effects (obesity, diabetes, cardiovascular morbidity) (Correll 2008, Vyas 2012, Findling 1998, Vitiello 2009).

Children appear to be at a higher risk of several adverse effects such as EPS of FGAs and the metabolic and endocrine adverse effects of SGAs (Vitiello 2009, McClellan 2013, Mattai 2010). Movement disorders (parkinsonism, akathisia, TD) may not only be an integral part of the schizophrenia process, but also emerge as side effects to antipsychotic treatment (Gebhardt 2008). Children tend to gain proportionately more weight and do so more rapidly during treatment compared to adults. Also the effects on plasma levels of prolactin may be more marked in adolescents. Drug induced metabolic changes can persist over time, they may not be fully reversible upon drug discontinuation, and the implications for long-term outcome can therefore be profound (Vitiello 2009, Mattai 2010). Thus, it is important that metabolic functions and risk factors are systematically monitored before and during the course of antipsychotic medication, and patients are advised regarding the importance of a healthy lifestyle including cessation of smoking and abuse, a healthy diet and routine exercise (McClellan 2013, Mattai 2010).

Efforts to evaluate and compare efficacy and side-effect profiles of different antipsychotic drugs have been performed in a few meta-analyses and guidelines within the recent years. A Cochrane review on antipsychotic treatment of psychosis in adolescents concluded that there was no convincing evidence that atypical antipsychotic medications were superior to typical medications (Kumra 2013). They found, however atypical antipsychotics to be more acceptable to young people because fewer symptomatic adverse effects were seen in the short term. The review found little evidence to support the superiority of one atypical antipsychotic medication over another for this patient group, but side effect profiles were different for different medications. An earlier Cochrane review on antipsychotic treatment for COS (Kennedy 2007) pointed to the superiority of clozapine in treatment resistant schizophrenia, but with considerable increased risk of adverse effects.

Practice parameters from the American Academy of Child and Adolescent Psychiatry (AACAP) (McClellan 2013) states that most atypical and traditional antipsychotic agents, with the exception of clozapine (that can only be used for treatment resistant schizophrenia spectrum disorders), can be used as primary treatment options for EOS. The choice of first line antipsychotic agent is dependent on side effect profile, comorbid conditions, past therapeutic response, patient and family preference, clinician familiarity, and cost (McClellan 2013, Kane 2010). AACAP recommend switching to another antipsychotic if insufficient effects are evident after a 6-week trial using an adequate dosage. They recommend that depot antipsychotics should only be considered in schizophrenic adolescents with documented chronic psychotic symptoms, and a history of poor medication adherence, since this formulation of the agents are not studied in the paediatric age groups and have inherent risks with long term exposure to side effects (McClellan 2013).

The NICE guidelines 2013 (Kendall 2013) rated the general evidence for antipsychotic treatment of EOP/EOS low to very low and found only minimal differences in efficacy among compounds (not including clozapine), but relatively large differences in side effect profiles.

In a meta-analysis, Ardizzone et al (Ardizzone 2010) could not demonstrate any superiority among the SGAs risperidone, olanzapine and aripiprazole concerning efficacy or all-cause discontinuation. However, aripiprazole had the lowest incidence of neuromotor adverse effects and weight gain.

Another meta-analysis reported that the response rate for FGA treatment was significantly higher and the risk of weight gain significantly lower compared to SGA treatment in EOS (Armenteros 2006). However, this study included older trials with patients diagnosed with childhood schizophrenia in which populations of schizophrenia and autism spectrum disorders were mixed together.

In conclusion, SGAs are regarded as first line treatment for EOS, but treatment has to be determined according to the balance between efficacy and sideeffects. Proper guidance of patient and caregivers before institution of treatment and regularly monitoring of side effects during treatment are important

6.2.2. Differential treatment effects on different symptom dimensions

In schizophrenia, the positive, negative and disorganized symptoms seem to follow independent courses over time (Arndt 1995, Eaton 1995, van Os 2009). Positive symptoms, especially hallucinations and delusions, often respond well to antipsychotic agents, whereas negative symptoms are more resistant to treatment (Stauffer 2012, Leucht 2009b, Marques 2011). It is unclear whether improvement of negative symptoms reflects a specific primary effect of treatment on negative symptoms or is secondary to an improvement of positive symptoms, a reduction of comorbid symptoms of depression or anxiety or alleviation of EPS due to previous therapy (Stauffer 2012). A study of drug-naïve adult patients with a FE of psychosis randomized to three different antipsychotics (Pelayo-Teran 2014) found five different trajectories for positive symptoms, three trajectories for the disorganized symptoms, and five trajectories for the negative symptoms, thus highlighting the markedly different patterns of response in the three different symptom dimensions.

6.2.3. Predictors of treatment response and outcome

6.2.3.1. Age of onset and gender

Response to antipsychotics in schizophrenia spectrum psychosis is highly variable, and determinants of response are not well understood. A study that examined patient- and trial-related determinants of outcome in adult schizophrenia, as measured by change on the Positive and negative syndrome scale (PANSS, Kay 1987) scores and study completion, in 29 placebo-controlled trials of 6 different SGAs (Rabinowitz 2014) found significantly better outcomes in female patients, young adult patients a few years beyond the FE, and patients with prominent positive or negative symptoms. Other studies in FE adult patients (Verma 2012, Faerden 2013, Stauffer 2011b) support the finding of better outcomes in female patients. Faerden et al. found better psychosocial functioning in females compared to males after 1 year (Global Assessment of Functioning, GAF) and Verma et al. found recovery at 2-years follow-up, predicted by female gender (Verma 2012), and Thorup et al. found in a 5-year follow up, that females had lower levels

of negative symptoms, were less likely to live alone and suffer from substance abuse, reached higher levels of social functioning and recovery and were more compliant with medication (Thorup 2014). Studies in chronic schizophrenia also found better outcomes in female patients (Stauffer 2011a, Ruberg 2011). In contrast to these finding, a study of treatment response trajectories (Levine 2010b) found a preponderance of males in the trajectory group with the best response.

Regarding age at onset as a predictor of treatment response and outcome, results are conflicting, but studies do not include children under the age of 13 years with COS. Rabinowitz et al. found that age at onset did not show a differential treatment response in adult schizophrenia across 29 placebo-controlled trials (Rabinowitz 2014). One study of treatment response trajectories in recent onset patients found, that members of the poor response trajectory had an earlier age at onset (Levine 2010a) and in another study in early onset patients (Crespo-Facorro 2007), earlier age of onset was significantly associated with less likelihood of response. Amminger et al. found younger age at onset significantly correlated with better symptomatic and functional outcomes after 2 years (Amminger 2011). A study of treatment response trajectories in FE patients found that members of better treatment response trajectories were characterized by being the youngest (Levine 2010b).

6.2.3.2. Comorbidity

Co-morbid depressive symptoms are reported with a prevalence of 17-83% in FE patients with a schizophrenia spectrum psychosis (Sonmez 2013), and are associated with an unfavourable disease course (Cotton 2012, Möller 2005).

A study in FE patients (Cotton 2012) found that patients with persistent depressive symptoms had significantly higher symptom scale scores (clinical global impressions scale-severity (CGI-S) score), a lower global function (GAF) and were less likely to be working at study end point (Cotton 2012). Riedel et al. found that depressed FE schizophrenia patients scored higher on all PANSS subscales both at admission and discharge (Riedel 2012) wheras Bottlender et al. found that depressive symptoms in the acute psychotic phase was a positive prognostic indicator concerning psychosocial functioning at discharge (Bottlender 2000). It has been speculated that early depressive symptoms experienced in the acute psychotic state might differ from depressive symptoms in the post-psychotic phase. In contrast to the “persistent depressive symptoms”, the acute depressive symptoms improve when psychotic symptoms resolve in response to antipsychotic medication (Oosthiuzen 2006).

Substance use may influence the onset and course of psychosis, and ongoing substance use is associated with negative outcomes (Sara 2014, Bertelsen 2009). Cannabis use is common among patients with schizophrenia spectrum disorders. In a study of adolescent patients more than 50% had cannabis use disorder at baseline (Schimmelmann 2012). Patients with cannabis use disorder had longer DUPs, higher illness severity and lower psychosocial functioning at baseline, but only patients with persistent cannabis use had worse outcomes and more service disengagement at discharge (Schimmelmann 2012). Pelayo-Teran et al. (Pelayo-Teran 2014) found longer cannabis use associated with higher scores and poorer responses in the positive and the disorganized dimension. A review study supports persistent cannabis use as a predictor of a worse outcome (Burns 2013). Burns et al. found that ongoing cannabis use disorder had an impact on perpetuating psychosis into a possibly progressive, relapsing and deteriorating disorder, especially in individuals with an underlying genetic and developmental vulnerability to schizophrenia spectrum disorders (Burns 2013).

6.2.3.3. DUP and premorbid functioning

As introduced above, a longer DUP has been associated with poor clinical and social outcomes in adults (Boonstra 2012, Chang 2012, Hill 2012, Marshall 2005, Verma 2012, Robinson 2004, Lambert 2010). The poorer outcome associated with longer DUP is reflected in a significantly unfavorable acute clinical response (Crespo-Facorro 2007, Crespo-Facorro 2013), higher scores and poorer responses in the positive dimension (Pelayo-Teran 2014), a lower rate of remission of positive symptoms, a lower rate of employment/occupation, a worse illness severity and worse global functioning at follow-up (Schimmelmann 2008) and a lower rate of long-term remission and recovery (Robinson 2004, Lambert 2010).

In line with these results in adults, a study in adolescents with FE schizophrenia (Fraguas 2014), found a longer DUP related to lower global functioning (GAF) at 2-year follow-up and less increase in global functioning from baseline to follow-up, and a shorter DUP significantly predicted clinical remission.

It is not known whether a treatment delay measured as longer DUP is causally related to a poorer outcome of illness, or if longer DUP is just a marker of an a priori poorer prognosis that may be determined by the underlying developmental psychopathology expressed by poor premorbid adjustment and causing both the delay in treatment and the poor outcome of illness regardless of the

treatment delay (Rund 2014). Thus a longer DUP has been significantly associated to worse premorbid function (Schimmelmann 2008).

Studies in FE adult patients found positive associations between premorbid function and treatment response (Rabinowitz 2006, Crespo-Facorro 2007, Crespo-Facorro 2013, Levine 2010a, Levine 2010c). Chang et al. found better premorbid adjustment in adult patients associated to sustained remission attainment after 3-year follow-up (Chang 2013). In line with these results, studies in EOP patients found a worse premorbid functioning to be associated with less improvement in global functioning (GAF) from baseline to follow-up (Fraguas 2014) and predictive of outcome at 1-year follow-up (Meng 2006).

6.2.3.4. Cognitive function and lack of insight

Studies in FE adult patients have found cognitive functioning, especially less impairment in verbal memory, positively associated with functional outcomes, remission and recovery at 1 to 5 years follow-up (Benoit 2014, Chang 2013, Gonzalez-Ortega 2013, Faerden 2013, Robinson 2004).

Long-term insight in psychosis (defined as the awareness of having a mental disorder, of its symptoms, its implications, and need for treatment) seems to be, to some extent, determined from first presentation, showing trait-like properties (Ayesa-Arriola 2014, Capdeville 2013). Poor insight is predicted by poor premorbid function, less severe depressive symptoms at baseline and a diagnosis of schizophrenia (Ayesa-Arriola 2014), and insight is found to be positively associated with remission (Capdeville 2013).

6.2.3.5. Response to treatment

As outlined above, response to treatment is important for short- and longterm outcome (Verma 2012, Levine 2010b, Agid 2013) and differences among antipsychotics in terms of effectiveness may determine a good adherence to treatment (Crespo-Facorro 2014). A study of treatment response trajectories in FE patients found that members of better treatment response trajectories had the lowest dropout rates from treatment (Levine 2010b). Antipsychotic response in schizophrenia varies according to stage of illness (Agid 2013). Studies in FE patients report initial response rates of 40-60%, whereas the chance of responding declines over time. Agid et al. found no notable effect of higher doses or switching to another SGA in FE schizophrenia patients (Agid 2013). Lower severity of symptoms at baseline has been sigficantly associated with less likelihood of an acute clinical response in FE (Crespo-Facorro 2007, Crespo-Facorro 2013) and in more chronic schizophrenia spectrum psychosis (Stauffer 2011, Ruberg 2011, Rabinowitz 2014). However, lower

baseline psychopathology scores predicted remission at endpoint in FE (Schennach-Wolff 2011, Emsley 2006b) and more chronic patients (Lambert 2010). A naturalistic study in FE psychosis patients found symptomatic response at 3 month predictive of long-term outcome at 2-years follow-up (Verma 2012).

6.2.4. Assessment of treatment response

Several clinical instruments and rating scales are used for the measurement of severity of psychotic symptoms and response to drug treatment. The CGI, the BPRS and the PANSS are widely used in clinical studies.

6.2.4.1. The clinical global impressions scale (CGI)

The CGI (Guy 1976) is a simple, 7-point scale. It is a valid clinical outcome measure suitable for routine use and has the advantages of being simple and not very time-consuming (Berk 2008, Leucht 2006b). The CGI consists of three different scales, the CGI-Severity scale (CGI-S), the CGI-Improvement scale (CGI-I) and the CGI-efficacy index. The CGI-S score assesses the clinician´s impression of the patient´s current illness state and the CGI-I score assesses the patient´s improvement or worsening (since the start of the study or initiation of medication). The rater is asked to consider his total clinical experience with the given population when evaluating the current severity of patient illness. The CGI-efficacy index relates therapeutic effects and adverse effects. It has been criticized that the psychometric properties of the CGI scale have never been well examined, that the scale does not provide information on specific aspects of psychopathology, that there are no anchors for scoring and that the scale may be too global to be sensitive for differences between two interventions. However the CGI scale has been validated in psychotic, mood and anxiety disorders and it has been shown to be as sensitive as the BPRS and the PANSS to detect efficacy differences (Leucht 2006b, Haro 2003, Berk 2008).

6.2.4.2. The brief psychiatric rating scale (BPRS)

The BPRS is a 18 item, 7 point rating scale (originally 16 items) measuring psychotic and non-psychotic symptoms (Overall 1974). The Brief Psychiatric Rating Scale for Children (BPRS-C, Overall 1982) is specifically developed for the assessment of psychopathology in children. The primary purpose defined in the development of the BPRS was to evaluate and assess treatment change in psychiatric patients while at the same time yielding a rather comprehensive description of major symptom characteristics (Nicholson 1995)

6.2.4.3. The positive and negative syndrome scale (PANSS)

The PANSS is based on two established psychiatric rating systems (the BPRS and the Psychopathology rating schedule (PRS, Singh 1975) and was conceived as an operationalized drug-sensitive instrument (Kay 1987). It is a 30 items, 7-point rating instrument. Seven items constitute a positive scale, seven items a negative scale, and the remaining 16 items a general psychopathology scale. Each item on the PANSS is accompanied by a complete definition that represents increasing levels of psychopathology.

The BPRS and the PANSS are based on semi-structured interviews, combined with observations of the patient´s behaviour and interactions, and information from carers or other informants. Both the BPRS and the PANSS have detailed anchor systems that should allow two different raters to come up with the same score, and the psychometric properties of the two rating scales have been evaluated. However, the PANSS and the BPRS are more time consuming that the CGI, though, which makes them less applicable in the daily clinical setting.

6.2.4.4. Equipercentile linking

Generally clinicians do not have time to conduct a full PANSS or BPRS rating in their daily clinical work. The BPRS and the PANSS scales have been related to the CGI-I scale via a method called equipercentile linking (Leucht 2006a, 2013). Equipercentile linking identifies those scores on both measures that have the same percentile rank in the same dataset. Linking analyses for both the BPRS and the PANSS based on large sample sizes, pooling individual patient data from several antipsychotic drug trials, have shown that a 20%-25% BPRS/PANSS reduction approximately means “minimal improvement” on the CGI-I scale, and 40-50% BPRS/PANSS reduction corresponds to “much improved” or “very much improved” on the CGI-I scale. It is, however, important to be aware that the variability of the finding is high and that it is only generalizable to drug trials of the same kind. Moreover linking studies have shown a time effect in the percentage BPRS reduction results, and the association of the BPRS/PANSS score reduction to the CGI-I depends on the symptom severity of the patient at baseline. Thus, a smaller objective percentage change is necessary for patients to be considered improved at earlier treatment weeks than at later, and less severely ill patients requires less BPRS/PANSS score reduction to achieve the same CGI-I score than more severely ill patients. The time effect might reflect that physicians expectations to the patient´s improvement are lower after short durations of treatment than at later stages.

6.3. Early response as predictor of the ultimate response

6.3.1. The dopamine hypothesis

The dopamine hypothesis of schizophrenia is based on the idea that dopamine neurotransmission in certain afflicted brain pathways are increased in this disorder. Studies provide evidence that the brain regions implicated in salience processing are dysfunctional in psychosis from the onset of the disorder, and that alterations in salience systems are linked to symptoms of psychosis (Winton-Brown 2014). Dopaminergic function in midbrain dopamine neurons and their projections to the ventral and dorsal striatum and temporal and frontal cortical regions are involved in salience processing (Winton-Brown 2014), and thus is important for salience processing in schizophrenia patients. The rate of dopamine synthesis progressively increases as patients develop psychosis, and the illness process possibly involves post-synaptic dopamine-receptors as well (Seeman 2013).

Antipsychotic drugs are dopamine-(D2) receptor antagonists (Agid 2003, Correll 2014, Kapur 2001, Grace 1997, Bunney 1978). In 1963 Carlson et al. demonstrated the accumulation of catecholamine metabolites in mouse brain enhanced by small doses of chlorpromazine and haloperidol (FGAs) (Carlson 1963). Administration of an antipsychotic drug (haloperidol) causes an acute (within minutes to hours) activation and greater firing in dopamine cells, whereas chronic administration (3 weeks) of an antipsychotic causes an increased activity of dopaminergic cells to the point where the great majority of the cells goes into apparent tonic ”depolarization block” (Bunney 1978). As the rapid time course of dopamine receptor blockade produced upon the administration of antipsychotic drug was not observed to correlate with the clinical actions of the drugs, which required weeks of treatment to become manifest, it has been argued that the therapeutic efficacy of antipsychotic drugs is due to their ability to induce a “depolarization block” (Grace 1997). These explanations of antipsychotic action formed the basis of the ”delayed onset of action” hypothesis of antipsychotic action (Agid 2003).

6.3.2. The hypothesis of early onset of antipsychotic effect

The “early onset of action” hypothesis suggests that the initiation of the antipsychotic effect begins simultaneously with the drug reaching its therapeutic levels (within the first few days), and that the effect accumulates over time and finally plateaus. In contrast to the ”delayed-onset” hypothesis there is no notable delay in clinical improvement, on the contrary there is more improvement in the earlier weeks than in later weeks (Agid 2003) (figure 1 in appendix I). Agid et al. point to an important distinction between delayed onset of action and a delayed realization of full

improvement. Although full therapeutic benefits take several weeks to realize, this by itself does not imply a delay in the onset of action. Studies have shown clinical improvement within days or even within 24 hours of the administration of an antipsychotic drug, which supports the ”early-onset” hypothesis (Kapur 2005, Agid 2003, Stern 1993, Stern 1994, McDermott 1991)

6.3.3. The early response in adult patients

In recent years, the time course of response to antipsychotic (AP) medication has attracted considerable interest (Agid 2003, Correll 2003, Leucht 2007, Leucht 2008, Kinon 2008, Kinon 2010). The focus has been on presence/absence of early improvement in the first few weeks after initiation of the antipsychotic treatment. In one study (Kapur 2005), a significant antipsychotic effect was shown to occur as early as within 24 hours of medication initiation, and a pooled analysis of double-blind studies including 7,450 patients showed greater improvement in the first two treatment weeks than in the subsequent two weeks (Agid 2003). These findings of early onset of AP action have been replicated and extended to one year of antipsychotic treatment during which also the greatest degree of symptomatic improvement occurred in the first 2-4 weeks (Leucht 2005a). Symptom improvement might take place a little later in subjects with a FE or recent onset psychosis, though, as results from adult studies in FE patients have found predictive improvement after as long as 6 weeks (Derks 2010), 8 weeks (Emsley 2006a) or 10 weeks (Gallego 2011).

It has been suggested that the early effects of antipsychotics are due to improvements in nonspecific symptoms, such as relief from anxiety and agitation, rather than a change in core psychotic symptoms. Studies have shown, however, that administration of an antipsychotic leads to an early and robust improvement in psychotic symptoms that is not secondary to drug-induced non-specific changes, since the improvement is seen independently on psychosis-specific items on the PANSS and BPRS scales (Agid 2003, Kapur 2005).

Early-onset AP response (ER)/non-response (ENR) has shown to be stable predictors of later clinical response/non-response and remission/non-remission in adults with FE or more chronic schizophrenia and across different antipsychotic medications (Leucht 2007, Leucht 2008, Ascher-Svanum 2008a, Chang 2006, Schennach-Wolff 2011, Agid 2003, Kinon 2008, Kinon 2010, Correll 2003). Studies have also found significant differences between early responders and early non-responders in other domains not directly related to symptom scores. These have included longer time to all-cause treatment discontinuation, lower overall and non-medication related treatment

cost, and higher levels of social and physical functioning in early responders (Liu-Seifert 2005, Ascher-Svanum 2008a).

6.3.4. Definition of treatment response, remission and early response.

"Response" to treatment can be defined as "a clinically meaningful improvement in a patient´s psychopathology, irrespective of whether the patient is still symptomatic or not" (Leucht 2009b). Definitions of response have usually been based either on the CGI-I-scale or on cut-offs in terms of percentage reduction of other more sophisticated scales as the PANSS or the BPRS.

"Remission" can be defined as "a state in which the patient is free of clinically significant symptoms" (Leucht 2009b). According to consensus criteria a patient is in "symptomatic remission" if eight items on the PANSS (delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal, lack of spontaneity) or seven items on the BPRS (grandiosity, suspiciousness, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect) are rated "mild" or less (3 or less) (Andreasen 2005). The remission is sustained if this threshold is maintained for at least 6 months (Andreasen 2005).

In most studies on early response, ER has been defined as ≥20% and ENR as <20% reduction on the PANSS or BPRS scales (Leucht 2008, Kinon 2008, Kinon 2010, Leucht 2014), but since studies have included different patient populations regarding duration of illness and used different response and remission criteria, no clear consensus has been reached on the definition and the predictive value of early response to AP medication (Schennach-Wolff 2010, Correll 2011).

Two weeks have been chosen as the early response assessment point in many studies (Stauffer 2011b, Kinon 2008, Kinon 2010, Leucht 2008, Leucht 2014, Hatta 2011) on the basis of previous investigations in which most of the improvement occurred in the first 2 weeks (Agid 2003, Leucht 2005a). However some studies in FE patients point to the importance of a later time point to determine early response status for this patient group (Derks 2010, Emsley 2006, Gallego 2011). In the study by Gallego et al., many of the participating FE patients responded between week 8 and 16.

6.3.4.1. Response trajectories

Estimates of response from early symptom changes have generally been based on a priori cut-off scores (percentage improvement) and on group means, which do not account for the heterogeneity within each group and the overlap between groups caused by inter-individual variation in drug

response. Furthermore the focus has been on early response at a particular time-point (Case 2011, Stauffer 2011b). To provide a more fine-grained appraisal, recent studies have focused on trajectories of response. Trajectories capture heterogeneity empirically by identifying subgroups that follow distinct treatment response patterns with time, avoiding predesignated subgroups. Moreover trajectory analysis uses all available information at each time point and identifies baseline characteristics that help distinguish to which subgroup a given individual may belong (Stauffer 2011a, Levine 2010b). Studies have identified 4 or 5 treatment response trajectories characterized by varying levels of symptomatic improvement (Levine 2010b, Levine 2010c, Stauffer 2011a, Case 2011, Marques 2011).

Methods like classification and regression tree analysis (CART analysis) have been used to identify what amount of change in which of the fewest PANSS symptom measures at the earliest time in treatment is most predictive of response or non-response at study endpoint (Ruberg 2011). By using CART analysis, Ruberg et al. created a 2-branch, 6-item decision tree (using early change in the scores of selected PANSS items), producing 3 distinct groups ("likely responders", "likely non-responders and "not predictable") (Ruberg 2011).

6.3.5. Early response in youth patients

One prior study in adolescents with early-phase schizophrenia found that early response after 3 weeks had the best predictive power for ultimate response at 6 weeks, and early responders were significantly more likely to achieve remission (Correll 2013). ER was defined as at least 20% reduction in the PANSS total score at week 2 or 3, whereas ENR decreased less than 20% in the PANSS total score. Ultimate responders had at least a 40% decrease in PANSS score at study end-point. Nearly 50% of the PANSS decrease was achieved by week 2, and up to 75% was achieved by week 3.

7. OBJECTIVES

The objectives of the current PhD-study are

1. To describe the phenomenology and outcomes of schizophrenia spectrum psychosis in children and adolescents.
2. To explore the predictive value of an early response of antipsychotic medication to predict later response in children and adolescents with schizophrenia spectrum psychosis.

8. METHODS

The empirical data collected for this thesis comprise a systematic review (paper I) and the analyses of the treatment response in two longitudinal clinical cohort studies (paper II and III)

8.1. Paper I

This study is a systematic review of studies describing the phenomenology of schizophrenia spectrum psychosis in children and adolescents. We searched for clinical studies published since 01/01/1990 and entered into the three databases PubMed/PsycInfo/EMBASE before August 7th 2014. The search terms and strategy was developed in collaboration with an experienced research librarian, based on a list of keywords and MESH terms, including: ”schizophrenia”, ”child”, ”youth”, ”adolescent”, ”psychotic/thought/paranoid disorder”, ”psychosis”, ”hallucination”, ”delusion”, ”perceptual/thought disturbance”, ”phenomenology”, ”first episode”, ”recent/early onset”, ”early detection”, ”early diagnosis”, ”early/childhood/adolescent onset schizophrenia”, ”early/childhood/adolescent onset psychosis ”, ”(treatment) outcome”, ”outcome assessment”, ”diagnostic stability” and ”course ”. The complete search strategy is provided in appendix II.

8.1.1. Included studies /populations

Studies were included in the review based on a set of inclusion criteria: >50% of participants with non-affective psychosis; b) age range/mean age <19 years; c) clinical samples recruited through mental health services; d) cross-sectional or prospective design; e) at least 20 participants at baseline; f) standardized/validated diagnostic instruments; g) quantitative psychotic symptom

frequency or severity scores data, and h) no study inclusion restriction based on thresholds for psychopathology.

Only prospective or cross-sectional studies were included to minimize ascertainment bias (from retrospective evaluations of diagnoses and psychopathology) and selection bias from unmeasured attrition during follow-up. We excluded data from clinical samples recruited through mental health services, and epidemiological studies of the general population were excluded. Reviews as well as studies of subjects with clinical high-risk states or with clearly substance-related disorders were also excluded.

8.1.2. Statistical analyses

Descriptive statistics were used to summarize the cohort, patient, illness and treatment characteristics, reporting weighted means ± SD and weighted proportions where appropriate. In longitudinal studies, we compared baseline psychopathology scores with endpoint ratings, using paired t-tests to assess if changes were significant over time. The following variables with at least 3 studies contributing longitudinal data were examined: PANSS total score, PANSS positive and negative symptom sub scores, CGI-S scores and CGAS/GAF scores.

Furthermore, we conducted exploratory correlational analyses testing the bi-variable associations between the following baseline variables: FE psychosis as opposed to mixed first-and multi-episode psychosis, gender distribution, age, age at illness onset, IQ, DUP, proportion with any psychiatric family history, primary diagnosis of schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified (psychosis-NOS), schizophrenia-spectrum disorders, bipolar disorder, and depressive disorder, as well as PANSS total score, PANSS positive, negative and general psychopathology symptom sub scores, CGI-S scores and GAF/ Children´s global assessment of functioning scale (CGAS, Shaffer 1983) scores at baseline. For exploratory analyses of factors influencing the change in psychopathology scores, all baseline variables were examined as potential moderators. The study duration and attrition were examined as potential confounding factors. Since most variables were non-normally distributed, we used non-parametric tests, i.e., Kruskall Wallis test for comparison of continuous variables across two categorical groups (i.e., FE versus mixed samples) and Spearman's rho for all other analyses testing correlations between continuous variables. All analyses were conducted in JMP 5.0.1, SAS Institute, Inc., 1989-2003, Cary, North Carolina), using two sided tests with the level of significance alpha set at 0.05.

8.2. The clinical studies (Paper II and III)

8.2.1. Study Design

The study for Paper II was conducted as part of the SATIETY (Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth) study (Correll 2009). The SATIETY study is an ongoing naturalistic cohort study of antipsychotic use in children and adolescents (aged 4-19 years) with psychosis, mood or aggressive spectrum disorder. Antipsychotic medication is based on clinician´s choice.

The study for Paper III was based on a post-hoc analysis of data from a multisite randomized placebo-controlled 6-week trial of olanzepine vs. placebo in 107 adolescents aged 13-17 years with schizophrenia (DSM-IV-TR) who were randomized 2:1 to olanzapine (n=72) or placebo (n= 35) (Kryzhanovskaya 2009).

8.2.2. Subjects

For paper II, we included 79 patients (aged 6-19 years) with schizophrenia-spectrum disorders according to DSM-IV treated with one of five different antipsychotic medications (not clozapine), who had at least one baseline and two post-baseline CGI-I assessments (at 4 weeks to assess ER, and at either 8 or 12 weeks to determine ultimate response (UR)), and confirmed AP adherence (by the measurement of AP blood levels).

For paper III, we included 69 patients (age 13-17 years) from the olanzapine treatment arm who had at least two post-baseline assessments (at either 2 or 3 weeks to assess ER, and at least one additional assessment to determine UR). The participants were inpatients and outpatients recruited from multiple sites in the United States (20 sites) and Russia (5 sites). A total score of 35 on the BPRS-C with a score of 3 or higher on at least one of the following 3 different BPRS-C items: hallucinations, delusions or peculiar fantasies were required for inclusion in the RCT.

8.2.3. Assessments

In paper II baseline assessments were obtained within 7 days of new AP initiation. Psychiatric diagnoses based on DSM-IV criteria, as well as race/ethnicity, past treatment history, and socioeconomic status (Hollingshead 1975) were assessed by chart review, discussion with treatment providers and clinical interview of the patient/caregiver. The CGI-S was used at baseline and monthly to rate illness severity, and CGAS was used to assess symptomatic and psychosocial functioning. Monthly CGI-I assessments were used to rate illness improvement during course of

treatment. At baseline and monthly subjects were assessed for height, body weight, fasting laboratory values, presence of extrapyramidal symptoms (EPS) (Simpson-Angus scale (SAS), Simpson 1970) and akathisia (Barnes akathisia scale (BARS), Barnes 1989).

In paper III, the schizophrenia diagnoses (DSM-IV-TR) were confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL, Kaufman 1997). The primary efficacy measure was the mean baseline to endpoint (6-weeks) change in BPRS-C total score. Other efficacy outcomes included changes in PANSS, CGI-S and the Overt Aggressions Scale (OAS, Yudofsky 1986) and remission. Improvement was evaluated with CGI-I at end-point. Safety outcomes included frequency of adverse events, and changes in body weight and metabolic measures. EPS were assessed by the SAS, the BARS and the Abnormal Involuntary Movement Scale (AIMS, Schooler 1982). Tests were performed at protocol-specified time-points, when clinically indicated, and when a patient completed the 6-week study period or discontinued early from the study. Fasting glucose and lipids were collected at baseline and endpoint.

8.2.4. Statistical analyses

In paper II, the primary outcome of interest was the sensitivity and specificity of ER/ENR for predicting UR/ UNR. The ER was defined as at least “minimally improved” on the CGI-I scale at week 4, and UR was defined as at least ”much improved” on the CGI-I scale at 12 weeks. Missing data were handled by the method of last observation carried forward (LOCF). The LOCF procedure is carried out as follows: For each individual, missing data values for a given variable are replaced by the last observed value of that variable. Once the data set has been completed in this way, it is analyzed, as if fully observed, i.e. under the assumption that data were missing at random.

For the primary outcome, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for patients with ER/ENR regarding UR using chi square tests for the overall 2x2 outcome table.

Sensitivity was determined as the proportion of ultimate responders who were correctly classified as early responders (“true positive”). Specificity was determined as the proportion of ultimate non-responders who were correctly classified as early non-responders (“true negative”). PPV was determined as the proportion of early responders who remained responders at end point and NPV was determined as the proportion of early non-responders who remained non-responders at end point.

As a secondary analysis, in paper II, the predictive value of ER/ENR status was evaluated in patient subgroups (schizophrenia/schizoaffective disorder/schizophreniform disorder vs. psychosis-NOS and AP-naïve vs. AP non-naïve patients) for UR/UNR as well as for changes in illness severity, functional status, treatment discontinuation, duration of inpatient stay and adverse effects.

ER and ENR pt. were compared on baseline values, using chi-square or Fisher's exact tests for categorical variables and t-test for continuous variables. As EPS and AP doses were larger in the ENR group, we also conducted an exploratory logistic regression analysis, investigating the effect of EPS on UR status, adjusting covarying for mean chlorpromazine equivalent doses. Finally we conducted a backward elimination logistic regression analysis of the effect of ENR on UR, entering ENR status, EPS during the 12-week treatment period and all baseline variables that were statistically significantly different between ER and ENR patients, as well as diagnostic subgroup and AP-naïve status in the initial model. For categorical variables remaining significant in this model, predicting UR, we further calculated number-needed-to-treat by dividing 1 by the difference between the two UR rates. All data were analyzed with JMP 5.0.1, were two-sided and alpha less than 0.05.

In paper III, we investigated the predictive accuracy of ER, when ER was defined as a ≥20% reduction in BPRS-C total score at week 2 (ER2) or week 3 (ER3) and ultimate response (UR) was defined as a percent BPRS-C total score reduction at study endpoint (week 6) of ≥20% (UR20), ≥30% (UR30), ≥40% (UR40) or ≥50% (UR50) (LOCF). Remission was defined at the end of the double-blind phase (LOCF), using the symptom severity component of the standardized remission criteria (Andreasen 2005). The time criterion (6 months) was not used owing to the study duration of 6 weeks. Sensitivity, specificity, PPV and NPV (defined as described above for paper II) were evaluated to determine the predictive accuracy of ER to predict UR and remission.

ER and ENR groups were compared with regard to patient demographics and illness characteristics at baseline, as well as for the proportionate weekly PANSS-total score change relative to the overall PANSS-total score change. ER and the ENR groups were also compared on the symptom scores and all-cause discontinuation, using chi squared test for categorical variables and t-test for continuous variables, respectively.

Logistic regression models for response and remission were performed using baseline variables only or baseline variables, ER status at week 2 or 3 and EPS post-baseline to examine which

demographic, illness and treatment characteristics predicted treatment response (defined a priori as ≥40% reduction in BPRS-C total score) or remission at endpoint.

To determine the BPRS-C total score improvement threshold at week 2 and week 3 with the best predictive power for ultimate response at week 6, receiver operating characteristic curves (ROC curves) were calculated for ER2 and ER3 regarding the BPRS-C total score reduction used to define the UR. Furthermore the best predictive power was examined for predicting ≥20%, ≥30%, ≥40% or ≥50% reduction in BPRS-C at week 6.

A ROC curve is a technique to establish the optimal cut-off point for a diagnostic test, in this case the cut-off point for the ER. The ROC curve was originally developed in the early days of radar and sonar detection during the Second World War (explaining the name: Receiver Operating Characteristic (ROC) Curve) to decide the optimal setting for detection of the largest ratio of signal to noise on the radar. The sensitivity (the true positive rate) and the specificity (the true negative rate) are calculated for all cut-off values of interest. The ROC curve is a graphical plot, where the X-axis is '1 minus the specificity', and the Y-axis is 'the sensitivity'. The diagonal line running from the lower left point (0.0) to the upper right point (1.1) reflects the characteristics of a test with no discriminating ability. The better the test discriminates true cases from true non-cases (in our case responders from non-responders), the closer it will approach the upper left corner. The area under the curve (AUC) is therefore an index of how discriminative the test is. A non-discrimination test has an AUC of 0.5, and the perfect test has an AUC of 1.

8.2.5. Ethics

Paper II: Informed consent was obtained from all subjects´ caregivers and from minors aged 9-17 years. The study was approved by the institutional review board of the North Shore-Long Island Jewish Health System (Correll 2009).

Paper III: Patients and their parents/authorized legal representatives signed an informed consent before the patients participate in the study.

9. SUMMARY OF THE RESULTS

9.1. Paper I. Phenomenology and outcomes of non-affective psychosis in children and adolescents: results from a systematic review and exploratory analysis of correlates.

Although 10-30% of adults with schizophrenia may have the first clinically significant psychotic episode before age 18, few studies have focused on the phenomenological characterization of children and adolescents with early-onset schizophrenia spectrum psychosis.

We conducted a systematic review of clinical studies of EOS published since 01/01/1990. Across 35 studies covering 28 independent samples (n=1506, mean age=15.6±1.9 years, mean age of onset=14.5±2.4 years; 62.3±10.8% male), the most frequent psychotic symptoms were auditory hallucinations (81.9%, other hallucinations=54.8%), followed by delusions (77.5%, distributed on persecutory=48.5%, referential=35.1%, grandiose=25.5%), thought disorder (65.5%), bizarre/disorganized behaviour (52.8%) and flat or blunted affect/negative symptoms (52.3%/50.4%), and 36% had disorganized/pressured speech. Mean PANSS-total, positive and negative symptom scores were 84.5±10.9, 19.3±4.4 and 20.8±2.9, and mean CGI-S and CGAS/GAF scores were 5.0±0.7 and 35.5±9.1 respectively. Across prospective studies (mean follow-up 2.2-years), symptoms and functioning improved significantly: PANSS-total (N=7, n=363): 84.5±10.8 to 60.8±5.1 (p=0.0006), CGI-S (N=4,n=283): 5.5±0.1 to 3.2±0.2, CGAS/GAF (N=6, n=349): 38.4±10.1 to 63.8±9.0 (p=0.0046). PANSS-positive and -negative baseline and change scores were significantly correlated within and across each other, while PANSS-total symptom and change scores correlated with positive and general symptoms, but not with negative symptoms. Schizophrenia-spectrum disorder was associated with less PANSS negative symptom improvement (p=0.0048). A diagnosis of affective psychosis was associated with a higher GAF/CGAS score at baseline (p<0.0001).

The data regarding insidious versus acute onset of psychosis was limited, but the two studies that reported on this, did find that a preponderance of EOS patients had an insidious onset (Asarnow 1994, Green 1992).

In the reviewed studies mean DUP was 17.2 months, ranging from only 2.2 months up to 45 months. The longest DUP of 45 months was found in a sample of pt. with a mean age of 9.9 years at onset of psychosis (David 2011). We found that a longer DUP was significantly associated with less improvement in global functioning (GAF/CGAS) (p<0.0001), and that a shorter DUP was marginally associated with samples of FE (vs. multi-episode) psychosis patients (N=9, 10.9±8.4 vs.

N=3, 32.1±13.8, p=0.052). The studies directly comparing EOP and AOP reported that EOP patients by far had by far the longest DUP (18.7 vs. 5.7 months).

Some of the included studies (N=7, n=397) reported individually (from their own analyses), that premorbid adjustment predicted increased illness severity and poor prognosis. A better premorbid adjustment significantly predicted remission, a better global and social function, and a better quality of life, whereas a worse premorbid adjustment significantly predicted more negative symptoms and a greater severity of the illness. A number of the included studies (N=4, n=188) also reported individually, that more negative symptoms at baseline significantly predicted a worse illness severity at follow-up, whereas less negative symptoms significantly predicted remission and a better social function.

A total of 32% of the patients had a family history of schizophrenia and 41% had a family history of any psychiatric disorder.

The proportion of patients with a schizophrenia diagnosis was higher at baseline (84 %) than at follow-up (72%), whereas the percentage of patients with affective disorder was higher at follow-up (24.5%) than at baseline (12.2%). Noticeably, the proportion of affective disorders doubled during follow-up. In terms of diagnostic transition, none of the shifts were significant.

A total of 32% of patients had a substance abuse and in the studies directly comparing FE EOP and AOP patients, almost 50% of EOP and 60% of AOP patients had a substance abuse. A total of 34% had a co-morbid diagnosis of PTSD.

9.2. Paper II. Early nonresponse determined by the clinical global impressions scale predicts poorer outcomes in youth with schizophrenia spectrum disorders naturalistically treated with second-generation antipsychotics.

The use of ER/ENR to antipsychotics as a predictor for UR/UNR may help clinicians to avoid lengthy continuation of inefficacious medical treatment.

In this 12-week treatment study, we investigated if the CGI-I could be used as marker of ER/ENR after 4 weeks of antipsychotic treatment in youth with schizophrenia-spectrum psychosis, and whether this measurement of the ER/ENR predicted the UR/UNR. We found that 45.6% of subjects were ER at week 4, and 54.4% were ENR. At week 12, 57% of subjects were UR. Patients were in average 15.2±2.8 years, predominantly male (58.2%), post pubertal (86.1%) and most patients had a diagnosis of Psychosis-NOS (63.3%) or schizophrenia (29.1%). Most patients were AP-naïve (77.2%). ER and ENR groups showed no differences regarding baseline demographic, illness and

treatment variables, except for an older age (p=0.034) and higher maximum risperidone dose (p=0.0043) in ENR patients. Mean CGI-S at baseline was 5.6±0.8 and mean CGAS was 34.0±8.8.

ER/ENR status at 4 weeks predicted UR/UNR at week 12 significantly (p<0.0001) with sensitivity=68.9%, specificity=85.3%, positive predictive value=86.1% and negative predictive value=67.4%. For pt. with a schizophrenia diagnosis and for AP-non-naïve patients the NPV (86.7% and 77.8% respectively) was higher than for the entire cohort of patients (that included a larger proportion of patients with Psychosis-NOS). ER patients had significantly better scores at every visit in CGI-I, CGI-S and CGAS (all p<0.0001).

More ER patients reached UR at week-12 compared to ENR patients (83.3% vs. 34.9%, p<0.0001). A significantly higher proportion of ENR patients had EPS at weeks 4, 8 and 12 (p=0.0019-0.0079). UR was independently associated with ER (OR=18.09, 95% confidence interval (CI) 4.71-91.68, p<0.0001) and psychosis NOS (OR=4.82, 95% CI 1.31-21.41, p=0.017) (p<0.0001). ENR and schizophrenia were associated with UNR. EPS was significantly associated with ENR (46.2% vs.12.2%, p=0.0018).

9.3. Paper III. Early response or nonresponse at week 2 and week 3 predict ultimate response or nonresponse in adolescents treated with olanzapine: results from a 6-week randomized placebo-controlled trial.

In adults with schizophrenia, ER/ENR to antipsychotics as soon as after 2 weeks is a robust predictor of UR/UNR. However, it is less clear whether the early antipsychotic response/non-response paradigm, including the threshold and time point for establishing ENR, is equally applicable to adolescents with schizophrenia.

In this 6-week trial, we found that already by week 2 and 3, olanzapine-treated youth (n=69) achieved 73.3% and 85.5% of their overall BPRS-C score reduction at 6 weeks (LOCF). ER and ENR patients did not differ significantly regarding baseline demographic, illness and treatment variables. The majority of patients were male, had an illness onset before age 13 and most had been treated previously with antipsychotics. At week 2, 68.1% of subjects were ER, and at week 3, 65.2% were ER.

ER2 and ER3 significantly predicted UR at week 6 (all p<0.0001), and significantly more ER2 and ER3 than ENR2 and ENR3 patients had remitted at study endpoint (p=0.039 to p<0.0001). The predictive value analyses of an early response of ≥20% reduction in BPRS-C total score at week 2 or week 3 for predicting UR and remission at week 6, showed that ER3 generally had slightly better

predictive power than ER2 for both UR and remission. The prediction of ER to UR (of ≥40% or ≥50% reduction in BPRS-C total score) showed high specificity (86%-100%) and PPV (91%-100%), whereas sensitivity (51%-74%) and NPV (46%-66%) were moderate. Regarding the prediction of remission, ER2 and ER3 showed moderate and somewhat lower predictive values than for UR. ROC curves showed, that a threshold for ER of ≥20% BPRS-C reduction had best predictive validity (area under the curve=0.88-0.92).

The logistic regression analysis showed that predictors of UR were ER2 (p=0.0001), ER3 (p<0.0001), a lower baseline AIMS score (0.041-0.044), a higher baseline SAS score (p=0.026), male gender (p=0.0075), and higher BPRS-C withdrawal score (p=0.026). ER2 (p=0.0044), ER3 (p=0.0003) and a lower baseline CGI-Severity score (p=0.0007-0.0013) predicted remission.

At 6 weeks, patients with ER2 and ER3 patients had significantly greater improvements in BPRS-C, CGI-I and CGI-S scores, and a higher proportion of remission and less all-cause discontinuation (p=0.047 to p<0.0001). Adverse event profiles were similar in ER and ENR groups, except for more baseline extrapyramidal symptoms (EPS) in ER3 than ENR3 patients (35.7% vs. 8.7%, p=0.02), and ER3 patients having a greater improvement in EPS compared to ENR3 patients (p=0.008)

Adolescents with schizophrenia experienced the majority of symptomatic improvement early during olanzapine treatment. ER predicted UR and remission, with ER3 showing the best predictive power. A ≥20% improvement threshold for defining ER was confirmed as a robust outcome indicator, regardless of cutoff for UR.

10. DISCUSSION

10.1. Summary of findings

The evidence base regarding developmentally sensitive descriptions of the phenomenology, course and outcome of schizophrenia spectrum psychosis (EOS) in children and adolescents is limited. In paper I, we reviewed prospective and cross-sectional studies of EOS patients diagnosed according to ICD-10 or DSM-III/IV and assessed with validated/standardized psychopathological instruments. To our knowledge no previous review of EOS systematically collected and analysed data on phenomenology across EOS samples worldwide.

In paper I, we confirmed some of the characteristics of EOS, reported in the literature. We found a male preponderance, a relatively long DUP, a high level of psychiatric family history (suggesting a high genetic load), a high level of premorbid difficulties, a high level of psychiatric co-morbidity and a relatively high proportion of patients with auditory hallucinations, thought disorder, disorganized behaviour, and negative symptoms. Both psychopathology scores and global function improved significantly over a mean follow-up of 2.2 years, however, data on long-term prognosis were limited. EOP patients had a longer DUP than AOP patients, and a longer DUP was significantly associated with less improvement in global functioning. A diagnosis of schizophrenia was significantly associated with less improvement in negative symptoms, and affective psychosis was associated with a better functioning at baseline. The ratio of patients with a diagnosis of schizophrenia spectrum psychosis was greater at baseline than at follow-up, whereas the opposite was true for affective psychoses, albeit shifts were not significant.

In paper II and III we found greater symptomatic improvement in the first 2-4 weeks than in the following weeks after initiation of treatment with a new AP in both EOS cohorts varying with regard to age, severity of diagnosis, prior exposure to AP, and the AP treatment under study (five different second-generation APs in paper I, and Olanzepine in Paper II). The key findings in both papers were that the ER/ENR at 2-4 weeks significantly predicted the UR/UNR and remission at study endpoint (after 12 weeks, and 6 weeks) thus replicating the results from studies in adult patients and extending them to EOS patients. In paper III a threshold for ER of ≥20% BPRS-C reduction at 3 weeks showed the best predictive power. In paper II, older age and EPS were associated with ENR, and ENR and schizophrenia were associated with UNR. In paper III, ER, male gender and higher BPRS-C withdrawal score predicted UR. In both studies, the ER was a robust and significant predictor of UR, even after adjustment for these other prognostic factors.

10.2. Strengths and limitations

In paper I, we decided to include only cross-sectional and prospective studies in the review to minimize ascertainment and selection biases as well as imprecisions in the recording of symptoms and diagnoses in retrospective studies. We made a comprehensive literature search and hand searched reference lists, and formulated detailed inclusion and exclusion criteria in order to be able to precisely decide which studies to include or exclude. All the included studies provided sufficient descriptions of the data collection process and used standardized, validated instruments for diagnostic evaluation and psychopathological examination. The included studies and the samples

differed with regard to age range, distribution of diagnoses, and psychometric instruments used for describing the patients symptoms and function. Moreover the data collected from the studies were spotty in nature, and the studies were small- to medium sized, which complicated the analyses, and made inferential statistics unsuitable. This heterogeneity most likely influenced the results of the explorative meta-analyses, meaning that the conclusions are preliminary and in need of future replication in large and more representative studies.

Data for Paper II had limitations in design compared to paper III, since the analyses were based on a naturalistic study, whereas Paper III analyses were based on a "state-of the art" randomized, placebo-controlled trial. The patient group was more homogenous in paper III than in paper II, because the age range was more narrow, and all patients had a diagnosis of schizophrenia, confirmed by a diagnostic interview (K-SADS-PL); whereas subjects in Paper II had schizophrenia spectrum disorders (primarily Psychosis–NOS), and their diagnoses were not confirmed by a diagnostic interview. Moreover, all patients in paper III were treated with the same AP, whereas they were treated with five different APs in Paper II. On the other hand most patients in paper II were AP-naïve, whereas most patients in paper III had already been exposed to AP medication before, which theoretically might influence the way, they responded to the medication. In paper II the more simple CGI scale was used as the sole measure of psychopathological symptoms (with no opportunity to compare this rating with more detailed PANSS/BPRS-ratings) and assessments were not undertaken until 4 weeks after baseline, whereas the more detailed BPRS-C scale was used in Paper III (together with both the CGI and the PANSS), and assessments were done at both week 2 and 3, allowing more detailed and fine-grained analyses and results. Data sampling for paper III was done at 25 different sites, which carries a risk of information bias, whereas data for paper II was collected at one site. Inter-rater reliability testing was performed in the study for Paper III, but not in the study for paper II. Both studies had a relatively low number of participants and allowed co-medication with other psychotropic drugs. The results in paper III may generalise primarily to the narrow group of EOS patients, with onset of illness in childhood and with prior exposure to AP whereas the results of the naturalistic study in paper II may better extrapolate to the daily clinical setting. The convergence of evidence from these two methodologically very different studies suggests that findings are rather robust, and may generalise to both clinical and research cohorts of patients with EOP.

I the following sections I will compare my results from the three papers with other studies of the phenomenology and outcome of early onset schizophrenia spectrum psychosis and the predictive

validity of the early antipsychotic response to predict the ultimate, clinically significant treatment response.

10.3. Demographics and clinical characteristics in EOS, paper I

Early onset schizophrenia spectrum psychosis is often characterized by a preponderance of males and an insidious onset. In paper I, patients had a mean onset of psychosis of 14.5 years, a mean age at baseline of 15.6 years and the male percentage was 62.3%, thus supporting the general findings of a preponderance of males. However, the preponderance of males in this patient group is challenged in a newer, Danish, register-based study that found an equal gender distribution among EOS patients in the period 1994-2010 (Okkels 2012).

We found longer DUP in EOP compared to AOP. Results from a review of 28 studies of FE psychosis estimated the DUP in AOP (Boonstra 2012) to be shorter than the DUP, we found for FE and multi-episode EOS. Others have found DUPs in EOS, to be considerably longer (1-7 years, Russell 1989, Maziade 1996, Eggers 1997, Häfner 1995, Alaghband-Rad 1995) than the range in the reviewed studies. A longer DUP was significantly associated with less CGAS/GAF improvement, emphasizing the potential importance of an early recognition of psychotic illness in order to improve long-term prognosis (Hill 2012, Chang 2012).

The literature generally suggests that EOS is characterized by have a stronger genetic liability for the disease than AOS (Masi 2006, Kumra 2001). We found that 32% of the EOS patients had a family history of schizophrenia, and 41% had a family history of any psychiatric disorder. Although family history of schizophrenia is the strongest single indicator of an individual schizophrenia risk, almost any other psychiatric disorder among first-degree relatives is shown to increase the risk of schizophrenia (Mortensen 2010). One study comparing rates of schizophrenia spectrum disorders (SPD) among parents of patients with COS, parents of patients with AOS and parents of community comparison subjects (Nicolson 2003), found that 25% of parents of COS patients were recorded with SPD, which was significantly higher than for parents of AOP patients who had a record of 11% SPD, and parents of comparison subjects, who had a record of 1.5% SPD. The finding of a familial history of schizophrenia in 32% of EOS patients is a little higher compared to the results from Nicolson et al., and may reflect selective reporting. Still, this finding points toward a strong genetic liability underlying early onset of the disorder.

In the literature EOP patients are reported to have severe premorbid developmental and behavioral dysfunction, and also to have more of these problems than AOP patients (Driver 2013, Cannon

2002, Cannon 2006, Paya 2013). Data from studies included in paper I (Schimmelmann 2007, Ballageer 2005, Joa 2009) confirmed this.

Studies of EOS patients are generally in lack of more detailed descriptions of the nature of the psychopathology, i.e. characterisation of hallucinations, delusions and formal thought disorders. In paper I we confirmed the general understanding that hallucinations in EOP patients are mostly auditory. The figures are roughly in accordance with other reports on EOP/EOS (Biederman 2004, Kolvin 1971, Green 1984, Russell 1989). We found a relatively high frequency of delusions (78%) compared to other studies reporting percentages of 54-63 % (Kolvin 1971, Green 1984, Biederman 2004, Russel 1989). We found preponderance of persecutory delusions (49%) and of delusions of reference (35%), which is also found in a study of adults with FE schizophrenia spectrum psychosis (Ellersgaard 2013). Patients with EOP are thought to have more disorganization and more formal thought disorder than AOP patients (Häfner 1995). We found that the vast majority (65%) of patients with EOP had formal thought disorder. One included study comparing EOP and AOP patients directly found formal thought disorder to be equally common in the two groups (Ballageer 2005). The frequency of formal thought disorder was close to the frequency reported by Russel et al. (Russel 1989), while two even older studies found very high frequencies of formal thought disorder (60% (Kolvin 1971), and 100% (Green 1984)).

A greater symptom improvement (as measured on the PANSS scale) was associated with higher baseline symptom severity scores, in line with results from studies in FE and more chronic adult patients (Crespo-Facorro 2007, Crespo-Facorro 2013, Stauffer 2011a).

Negative symptoms were present in half of the EOP patients in paper I. Negative symptoms were reported to be more common in EOP than in AOP patients by two of the included studies that compared these patient groups directly (Pencer 2005, Ballageer 2005). The prevalence of negative symptoms is estimated at approximately 15% in FE adult patients and 25%-30% in chronic adult patients with schizophrenia (Foussias 2010). Compared to these percentages in adult patients, the patients in our sample do seem to have negative symptoms more often, but the contributing number of patients and studies were small. The EOP patients had a moderate level of negative symptoms at baseline, with less reduction at follow-up, compared to the positive symptoms. The level of negative symptoms probably is of great importance. In our analyses we found a diagnosis of schizophrenia associated with less improvement in negative symptoms. The included studies reported individually (from their own analyses), that more negative symptoms at baseline significantly predicted a worse illness outcome. These findings are consistent with results from

adult studies (Fenton 1991, Möller 2010, Foussias 2010, Carbon and Correll – in press). Negative symptoms are generally difficult to treat effectively, and recent studies have shown that negative symptoms could play a central role in the process of recovery from schizophrenia and in the long-term prognosis of the disease (Strauss 2010, Austin 2013).

10.4. Comorbidity, diagnostic stability and prognosis in EOS, Paper I

The lower proportion of patients with schizophrenia spectrum disorders at follow-up compared with the proportion at baseline, and the higher proportion of patients with affective disorder at follow-up also compared with the proportion at baseline, may indicate a predominant pattern of diagnostic shift from schizophrenia spectrum disorder to affective disorder, although such shift could not be directly assessed. Reports in the literature (Salvatore 2009, Driver 2013), do suggest a differential diagnostic error at baseline misclassifying more mood disorders as schizophrenia, than vice versa. On the contrary, another study found the predominant pattern of shifts was towards schizophrenia spectrum disorder (Chang 2009). None of the diagnostic shifts reached significance in paper I, but data were limited.

We found a high rate of comorbidity in EOP patients, which is also reported in other studies of youth patients (Driver 2013, Ross 2006). Specifically we found a high proportion of patients with co-morbid ADHD, PTSD and substance abuse. In a Danish randomized clinical trial with adults suffering from FE schizophrenia spectrum psychosis, 27% had substance abuse (Petersen 2007), and another study in FE adolescent patients found baseline cannabis use disorder in 53% of the patients (Schimmelmann 2012). The data suggest that substance abuse is very common in patients with schizophrenia spectrum psychosis, but the percentage probably varies a lot between different samples. The relatively high co-morbidity with PTSD (34%) supports the notion that trauma plays a role in the pathogenesis of early onset psychosis (Dvir 2013, Harley 2010, Varese 2012, Li 2014, Aas 2014).

Patients were moderately to markedly ill and globally impaired at baseline, but they improved significantly over time. Newer studies (also included in the review), primarily from early intervention services, showed either no differences in outcome between EOP and AOP patients (Schimmelmann 2007) or an even better outcome in EOP compared to AOP patients (Amminger 2011). In contrast newer reviews (Remschmidt 2012, Clemmensen 2012) concluded that outcome in EOS is much worse than in AOS patients. It might be, that outcomes for adolescent onset psychosis have improved in recent years due to a greater focus on early identification and phase

specific treatment. On the other hand, the fact that early intervention programs focus on a broader psychosis spectrum, whereas Remschmidt et al. focused on patients with a diagnosis of schizophrenia, may explain some of the differences in outcome. Moreover, early intervention programs usually do not include children, who on average have longer DUP, more premorbid developmental difficulties, a higher genetic load and probably a poorer outcome. Remschmidt et al. found that all studies of COS, defined as onset of schizophrenia before 13 years of age, revealed a highly unfavourable course of COS in comparison to other studies of EOS patients with later onset of illness (Remschmidt 2012). The group of childhood onset schizophrenias are rare diseases making it difficult to study whether an intensified, developmentally sensitive treatment program may be able to improve outcome in this age group.

10.5. Early response to predict later response in youth treated with antipsychotic medication, Paper II and III

Treatment with AP medication is recommended in children and adolescents with psychosis, but it is not nearly as well documented as in adults, and children and adolescents are more vulnerable to adverse effects of the medication. To evaluate antipsychotic response, treatment with AP medication is usually continued for at least 4-6 weeks in clinical practice (Kane 2003) and the lack of biomarkers for AP response (Carbon and Correll, in press) makes the use of early response patterns an attractive tool to guide clinicians in decisions regarding the timing of continuation or abortion of AP treatment in the individual patient.

In paper II and III we conducted post-hoc analyses of data from studies of EOS patients treated with antipsychotic medication. In paper II we found ER at 4 weeks (defined as a CGI-I score of at least "minimally improved") to predict UR at week 12, and in paper III we found ER/ENR at week 2 or 3 (defined as ≥20% reduction in BPRS-C total score) to be a robust and significant predictor of UR and remission at 6 weeks. These findings are in line with results from studies in adults suffering from a FE or more chronic schizophrenia (Agid 2003, Correll 2003, Leucht 2007, Correll 2013, Leucht 2008, Kinon 2008, Kinon 2010, Ascher-Svanum 2008a, Stauffer 2011b, Hatta 2011) where ER reliably predicted UR and remission at study endpoint. There is only one additional study reporting on early antipsychotic effects to predict later effects of AP medication in youth (Correll 2013). The study is a post hoc analysis of data from a RCT of aripiprazole vs. placebo for adolescents with schizophrenia, and ER was defined as at least 20% reduction on PANSS total

scores at week 2 or 3. Similar to our results in paper III, this study found that ER predicted UR and remission, and that ER at week 3 showed the best predictive power for UR at 6 weeks.

The participants in Paper II differed from patients in both paper III and the study by Correll et al. (Correll 2013) in several ways. Patients in paper II were AP-naïve children and adolescents with FE schizophrenia spectrum psychosis (not more narrowly defined schizophrenia) and were naturalistically treated with one of five different AP medications, and the treatment response was rated on the CGI scale, whereas participants in Paper II and the study by Correll et al 2013 were adolescents with a diagnosis of schizophrenia, treated with one AP according to the study protocol and AP effects were rated with PANSS, BPRS-C and the CGI scales. In spite of the variations in participants, design and measurements across the three studies, the results converge and confirm the predictive value of ER/ENR for the later clinically significant response to AP medication also found in adult studies. Furthermore, evidence from both paper II and paper III, clearly show that the majority of symptom improvement occurs within the first 2-4 treatment weeks. This mirrors the findings in adult studies and in the study by Correll et al. (Correll 2013, Agid 2003, Leucht 2005a).

The majority of participants in paper II are FE patients in contrast to patients in paper III. FE adult patients have in some studies shown a tendency to respond later than more chronic samples (Gallego 2011, Emsley 2006a, Derks 2010) and treatment response trajectories in early onset patients found earlier age of onset significantly associated with poorer response (Crespo-Facorro 2007, Levine 2010c). The early response frequency was 46% by week 4 in paper II and 65% by week 3 in paper III. Thus FE patients in paper II do seem to respond a little later than patients in paper III.

However, the frequency of ER of 68% at week 2 and 65% at week 3 in paper III is quite high compared to the study of adolescents treated with aripiprazole by Corell et al, where the frequencies were 33% and 49% at week 2 and 3 respectively. An ER frequency of 65% is also high compared with studies in adult FE patients (Stauffer 2011b, Emsley 2006a), which found ER in 43-47% of patients, and more chronic adult schizophrenia studies, which found ER frequencies of 22-30% (Kinon 2008, Kinon 2010, Ascher-Svanum 2008). These differences might be related to differences in pre-baseline exposure to antipsychotics, and the degree of required washout, or to differing levels and/or time course of efficacy between different antipsychotics.

The ROC analysis performed in paper III showed that a threshold for ER of ≥20% BPRS-C reduction had the best predictive values to predict UR. According to equipercentile linking (Leucht 2005b) this is comparable to “minimal improvement” on the CGI-I scale, the threshold used in

paper II to define ER. In line with our results from paper III, Stauffer et al. (in FE adult patients), using a data-driven approach, found that a cut-off point of 26.2% improvement on the PANSS total score (at week 2) had the optimal predictive values for the treatment response status at study end-point (week 12) (Stauffer 2011b)

We analysed specificity, sensitivity, PPV and NPV for the prediction of response (paper II and III) and remission (paper III) at study end point. A high specificity and NPV are needed to avoid unnecessary changing of AP medication in patients who would have responded ultimately. In both paper II and paper III the prediction of response status at end-point had high specificity and PPV, whereas NPV and sensitivity were only moderate. These results indicate a moderate probability that non-responders at study endpoint were correctly identified by the early non-response, but also that this ENR at 2-4 weeks might not suffice to reliably identify youth patients who will not benefit from longer treatment with the antipsychotic. In paper II, NPV were higher for AP non-naïve patients, and patients with a diagnosis of schizophrenia, indicating that ENR may have more predictive value in patients with a schizophrenia diagnosis, and in patients with prior exposure to AP medication, as indicator of ultimate response. These results from paper II are in line with studies in adult schizophrenia patients, where the predictive value of ENR at 2 weeks in FE schizophrenia samples was generally not as good as seen in more chronic samples (Gallego 2011, Emsley 2006a, Stauffer 2011b).

In study III multivariate regression analysis confirmed that ER remained a robust and significant predictor of UR and remission. In addition, higher BPRS-C withdrawal and male sex predicted a larger treatment response, whereas lower baseline CGI-S score predicted remission. Studies in adults also found the early response and higher baseline psychopathology scores to be a predictive of UR, whereas lower baseline psychopathology scores predicted remission at endpoint (Schennach-Wolff 2011, Crespo-Facorro 2007, Emsley 2006b). In our study, only higher baseline BPRS-C withdrawal scores were associated with greater response. Our finding of male sex as a predictor of UR is in contrast to the general association of male sex with poorer antipsychotic response (Verma 2012, Faerden 2013, Stauffer 2011b), though recent findings have been more heterogeneous (Carbon and Correll – in press).

In our studies, we investigated the relation between treatment responsiveness and EPS. We found (paper II) that ENR patients had more extrapyramidal symptoms (EPS), whereas in paper III adverse event profiles were similar for ER and ENR, except that patients cathegorized as ER patients at week 3 had more baseline EPS *and* a greater improvement in EPS compared to ENR

patients. In the study by Correll et al., even though ER patients had similar or lower adverse events rates than ENR, ER patients showed greater self-reported Parkinsonism.

The literature indicates that movement disorders (MD) may represent trait characteristics of schizophrenia and mark an increased risk of AP-induced MDs such as EPS. In a FE study of AP-naïve patients with schizophrenia (age range 16-40 years), subjects with presence of extrapyramidal symptoms already at baseline had more negative symptoms and were subsequently more likely to develop parkinsonian side effects after 8 weeks of treatment compared to patients without baseline extrapyramidal symptoms. Furthermore, their treatment response was poorer (Chatterjee 1995). Also, increased severity of AP-induced MDs may be associated with a poorer outcome of schizophrenia. For instance, tardive dyskinesia has been associated with less antipsychotic efficacy and poorer treatment outcomes (Ascher-Svanum 2008b), and in a naturalistic study of adolescents with more chronic schizophrenia treated with different APs, patients with AP-induced MDs showed more pronounced psychopathology (Gebhardt 2008). Specifically, severity of AP induced Parkinsonism and dystonia correlated with negative symptoms, while akathisia correlated with hostility and suspicion. In this study, patients with AP-induced MDs were significantly younger at onset of schizophrenia and at onset of AP treatment (Gebhardt 2008). The finding that akathisia (which may be more related to the noradrenergic transmitter system (Wilbur 1988)) was associated with hostility and suspicion as in the Gebhardt study has not been reported in other studies and was not specifically tested in our studies. Akathisia alone, was not related to ENR or UNR in our or prior studies. In one study of chronically ill schizophrenia patients (Kinon 2010), EPS was not related to ENR or UNR (similar to our findings in paper III), whereas EPS was related to UNR in an earlier study of FGAs (Kinon 1993), and EPS was related to both ENR and UNR in a study of FE patients (Stauffer 2011b). In the latter study, both the ER and the ENR group had a significant worsening of Parkinsonian symptoms early on. In the last 6 weeks, EPS improved in responders, but not in non-responders, and significant between-group differences were seen at week 10 and 12.

To summarize, several (but not all) studies display converging evidence of associations between the presence of primary MDs, AP-induced EPS, psychopathological severity, and impaired treatment response, all suggestive for dopamine dysfunction, that is uncovered by EPS in response to antipsychotic treatment and mark both ENR and UNR, probably especially in the early phase of the illness and in antipsychotic-naïve patients.

In paper II CGI-I assessments were used to rate illness improvement during the course of treatment. Less severely ill patients require less BPRS/PANSS score reduction to achieve the same CGI-I

score than more severely ill patients. This could mean that some early effects might be missed in the more severely ill patients when the CGI-I is used alone. In paper II we demonstrated a robust effect of ER/ENR to predict UR/UNR when using the CGI scale as the only psychopathological rating scale in children and adolescents. These results are promising for the utility of the CGI-scale based early decision making in clinical settings, but this requires further consideration and study.

11. CONCLUSION AND PERSPECTIVES FOR FURTHER RESEARCH

The phenomenology of early onset schizophrenia spectrum psychosis is not well described in prospective studies. Our systematic review confirmed and extended the evidence of the characteristics of EOS patients as compared with AOS patients. Youth were seriously impaired, but improved over time. Data on long-term outcomes of EOS are conflicting, but the prognosis of the disorder might have improved in recent study years for adolescence.

Treatment of children and adolescents with antipsychotic medication presents unique considerations for a number of reasons. Pharmacotherapeutic treatment may influence brain development during critical periods of childhood and adolescence, and while treatment is often warranted treatment for many years in order to control psychotic symptoms, youth are also at a higher risk of side effects. We found that early response and nonresponse to antipsychotic treatment were stable and robust predictors of ultimate response, nonresponse and remission, and we thus replicated findings from adult studies and extended them to youth patients.

The use of the CGI scale as a psychopathological assessment tool in clinical and research settings seems promising, though results needs to be replicated in future studies. In research studies the CGI scale should preferably be complemented with one of the more detailed psychopathology scales to be able to describe the patients more detailed and to compare the different scales. However, the same raters should not rate both the CGI and the more detailed psychopathology scales, because of the risk of conflating the two, and to be able to independently assess the performance of the much used CGI scale that is a feasible clinical assessment tool.

The data from the TEA-study will be analysed in the near future, and we will have a chance to look at the patients´ psychopathological symptoms, their side effect profiles and the predictive values of the early effects of AP treatment (either aripiprazole or quetiapine) to predict later, clinically

significant effects at 12 weeks, and clinical and functional outcomes at the one-year follow-up. Moreover, we will compare ratings on the CGI and the PANSS scale from the same patients at the same time-points.

There is a need to further investigate early onset schizophrenia spectrum disorders in large and representative, prospective studies to expand the knowledge base necessary to improve the early and developmentally sensitive treatment of EOS including optimised AP treatment guided by the patients` individual profile of symptoms, and the early treatment response.

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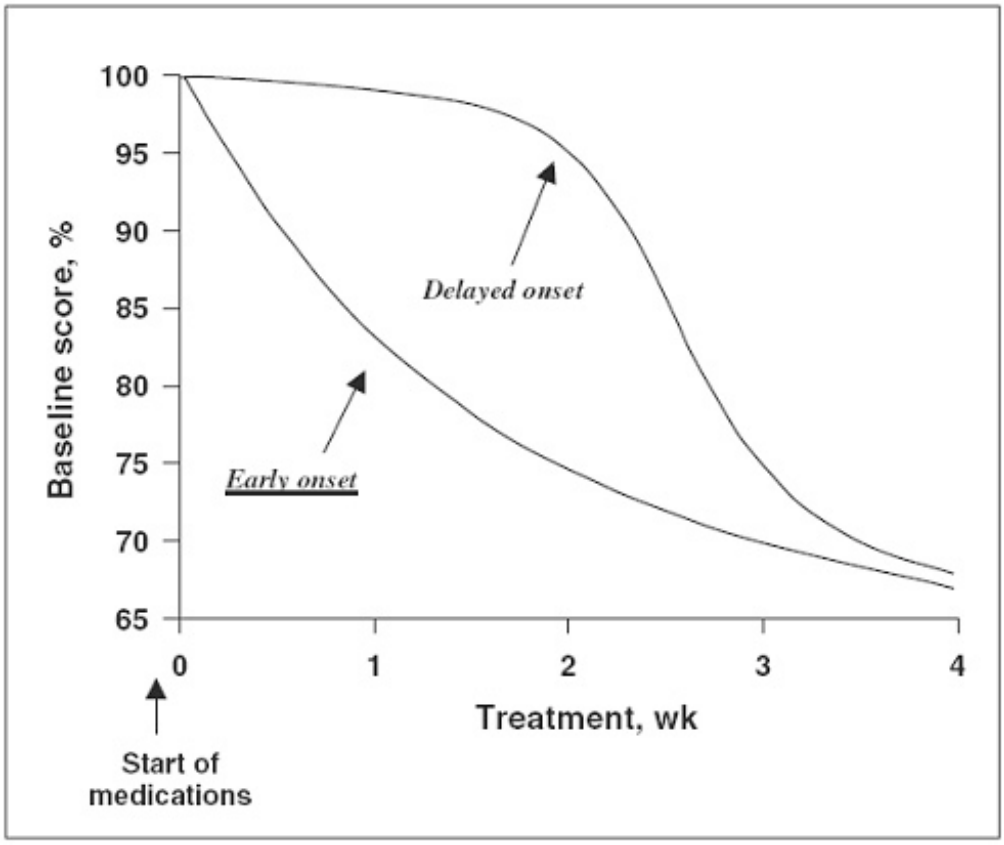
13. APPENDIX I



14. APPENDIX II

Search strategy, paper I

We searched the databases PubMed, PsycInfo and EMBASE and hand searched reference lists of eligibel papers and pertinent reviews for studies published since January 1st, 1990 reporting non-retrospective data in children or adolescents with a diagnosis of predominantly non-affective psychosis using the following search criteria:

PubMed:"Schizophrenia"[Mesh] OR schizophren* **AND** child[MeSH Terms] OR child, preschool[MeSH Terms] OR child* OR child OR adolescent[MeSH Terms] OR adolescen* OR youth OR adolescent **AND** "thought disorder" OR thought dis* OR psychos* OR psychotic disorders[MeSH Terms] OR schizophrenia and disorders with psychotic features[MeSH Terms] OR (psychot*OR "psychotic disorder" OR paranoid disorders[MeSH Terms] OR "paranoid disorder" OR paranoi* OR hallucinations[MeSH Terms] OR hallucination OR hallucinat* OR delus* OR delusion OR delusions[MeSH Terms]) OR phenomenology* **AND** "first episode" OR "recent onset" OR "early onset" OR "early detection" OR "early diagnosis" OR early diagnosis[MeSH Terms] OR schizophrenia, childhood[MeSH Terms] OR "early onset schizophrenia" OR "adolescent onset schizophrenia" OR "childhood onset schizophrenia" OR "early onset psychosis" OR "childhood onset psychosis" OR "adolescent onset psychosis" **AND** treatment outcome[MeSH Terms] OR outcome assessment[MeSH Terms] OR outcome* OR "diagnostic stability" OR course*

EMBASE: exp schizophrenia OR schizophren*.mp. AND exp child OR youth.mp. OR adolescen*.mp. OR child*.mp. OR exp juvenile **AND** "first episode".mp. OR "recent onset".mp. OR "early onset".mp. OR "early detection".mp. OR "early diagnosis".mp. OR early diagnosis OR "early onset schizophrenia".mp. OR "childhood onset schizophrenia".mp. OR "adolescent onset schizophrenia".mp. OR "early onset psychosis".mp. OR "childhood onset psychosis".mp. OR "adolescent onset psychosis".mp. **AND** exp treatment outcome OR exp outcome assessment OR outcome*.mp. OR "diagnostic stability".mp. OR course*.mp. **AND** exp psychosis OR hallucinat*.mp. OR delus*.mp. OR phenomenology*.mp. OR paranoi*.mp. OR thought dis*.mp. OR psychos*.mp. OR psychot*.mp. OR "psychotic disorder".mp.

PsycInfo:exp schizophrenia OR schizophren*.mp. **AND** child*.mp. OR adolescent*.mp. OR youth.mp. **AND** outcome*.mp. OR course*.mp. OR "diagnostic stability".mp. OR exp treatment outcomes OR outcome assessment.mp. **AND** "childhood onset psychosis".mp. OR "childhood onset schizophrenia".mp. OR "adolescent onset psychosis".mp. OR "early onset psychosis".mp. OR

"early onset schizophrenia".mp. "childhood onset schizophrenia".mp. OR "adolescent onset schizophrenia".mp. OR "first episode".mp. OR "recent onset".mp. OR "early onset".mp. OR "early detection".mp. OR "early diagnosis".mp. **AND** "thought disorder".mp. OR thought dis*.mp. OR psychos*.mp. OR psychot*.mp. OR "psychotic disorder".mp. OR "paranoid disorder".mp. OR paranoi*.mp. OR hallucination.mp. OR delusion.mp.OR hallucinat*.mp. OR delus*.mp. OR phenomenology*.mp. OR exp psychosis OR exp perceptual disturbances OR exp thought disturbance

The last search was performed on August 7th 2014.

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16. PAPERS

PAPER I

Text: 5951 words

Abstract: 300 words

Tables: 8

Figure: 1

Phenomenology and outcomes of non-affective psychosis in children and adolescents: results from a systematic review and exploratory analysis of correlates

Marie Stentebjerg-Olesen[1,2], MD; Anne K. Pagsberg[1,2], MD; Anders Fink-Jensen[3,4], MD; Christoph U. Correll[5,6,7,8] MD & Pia Jeppesen[1,2], MD

Institutional Affiliation:

[1] Child and Adolescent Mental Health Center, Mental Health Services, the Capital Region of Denmark;

[2]Faculty of Health Science, University of Copenhagen, Denmark

[3] Mental Health Centre, Copenhagen, Copenhagen University Hospital, Denmark

[4]Laboratory of Neuropsychiatry, Department of Neuroscience and Pharmacology, University of Copenhagen

[5]The Zucker Hillside Hospital, Department of Psychiatry, North Shore - Long Island Jewish Health System, Glen Oaks, New York, USA;

[6] Hofstra North Shore-LIJ School of Medicine, Hempstead, NY, USA;

[7] The Feinstein Institute for Medical Research, Manhasset, New York, USA;

[8] Albert Einstein College of Medicine, Bronx, New York, USA;

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Drs. Stentebjerg-Olesen, Pagsberg and Jeppesen have no conflicts of interest to report.

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Corresponding author: Pia Jeppesen, MD, address, phone and email

Abstract

Background:

Although 10-30% of adults with schizophrenia start having psychotic symptoms before age 18, data about the phenomenology and outcome in youth are scarce.

Methods:

Systematic review of studies published from 01/01/1990-08/07/2014 including studies with a) ≥50% non-affective psychosis; b) mean age <19 years; c) clinical samples recruited through mental health services; d) cross-sectional or prospective design; e) ≥20 participants at baseline; f) standardized/validated diagnostic instruments; g) quantitative psychotic symptom frequency or severity data. Exploratory analyses assessed associations between relevant clinical variables.

Results:

Across 35 studies covering N=28 independent samples (n=1506, age=15.6 years, age at illness onset=14.5 years; male=62.3%; schizophrenia-spectrum=89.0%), the most frequent psychotic symptoms were auditory hallucinations (81.9%; any: 70.3%, other: 54.8%), delusions (77.5%; mainly persecutory (48.5%), referential (35.1%), and grandiose (25.5%)), thought disorder (65.5%), bizarre/disorganized behaviour (52.8%) and flat or blunted affect/negative symptoms (52.3%/50.4%). Mean Positive and Negative Syndrome Scale (PANSS)-total, positive and negative symptom scores were 84.5±10.9, 19.3±4.4 and 20.8±2.9; mean Clinical Global Impressions-Severity and Children's Global Assessment Scale/Global Assessment of Functioning (CGAS/GAF) scores were 5.0±0.7 and 35.5±9.1. Across prospective studies (2.2-years), symptoms/function improved significantly: PANSS-total (N=7, n=363): 84.5±10.8 to 60.8±5.1 (p=0.0006), CGAS/GAF (N=6, n=349): 38.4±10.1 to 63.8±9.0 (p=0.0046). PANSS-positive and negative baseline and change scores were significantly correlated within and across each other, while PANSS-total symptom and change scores correlated with positive and general, but not with

negative symptoms. Longer duration of untreated psychosis (DUP) was associated with less CGAS/GAF improvement ($p<0.0001$); schizophrenia-spectrum disorder was associated with less PANSS negative symptom improvement ($p=0.0048$). Five samples directly comparing early-onset with adult-onset psychosis found longer DUP in EOP (18.7±6.2 vs. 5.4±3.1 months, $p=0.0027$).

Conclusions:

Youth with schizophrenia-spectrum disorders are impaired, but improve over time. Longer DUP in EOP, which was associated with poorer CGAS/GAF improvement , emphasize the need for early detection and treatment of psychosis in youth.

Background

Up to one-third of adults suffering from psychotic disorders experience onset of clinically significant psychotic symptoms before adulthood (Young 2004, Amminger 2006). Childhood-onset psychotic disorders before the age of 13 years are rare, but there is a considerable increase in the prevalence during adolescence (Remschmidt 1994, Vyas 2011, Pedersen 2014).

Early-onset schizophrenia (EOS) is defined by illness onset before 18 years of age, and a sub-group with onset before age 13 is usually referred to as very-early-onset schizophrenia (VEOS) or "pre-pubertal" schizophrenia (Masi 2006, Werry 1992). Since the appearance of DSM-III and ICD-9, schizophrenia patients with an early onset are diagnosed using the same criteria as for adults. Schizophrenia-spectrum disorders display largely overlapping characteristics and presentations, regardless of the age at onset, and overall have a high diagnostic stability from childhood throughout adolescence and adulthood (Masi 2006, Remschmidt 2012). Therefore, diagnostic criteria are arguably age-independent.

However, the evidence base is limited regarding developmentally sensitive descriptions of the phenomenology, course and outcome of EOS. Textbooks and reviews often refer to a limited number of studies, in which EOS, as compared to adult-onset schizophrenia (AOS), is characterised by a preponderance of males, an insidious onset (especially in VEOS), less complex or elaborated delusions, hallucinations affecting several sensory modalities, more negative symptoms, disorganisation and formal thought disorders, a higher frequency of premorbid neurodevelopmental abnormalities, a stronger biological disposition, and a poorer prognosis due to a more severe and early disruption of brain development (Asarnow 1994, Werry 1992, Masi 2006, Remschmidt 1994, Remschmidt 2012).

Apparently, there is considerable overlap in phenomenology between schizophrenic and affective symptomatology in children and adolescents with psychosis, and the clinical picture in youth may become clear only with time, making the differential diagnosis between schizophrenia and affective disorders with psychotic symptoms difficult, and the treatment strategy complicated. The most common mistake seems primarily to involve a misclassification of mood disorder as schizophrenia (Werry 1992, Masi 2006). The diagnostic challenge of psychosis in childhood and adolescence extends to the differentiation of schizophrenia from pervasive developmental disorder, severe

personality disorders/traits, post-traumatic stress disorder, generalized anxiety disorder and obsessive-compulsive disorder without insight (Driver 2013, McClellan 2013). Children with complex neurodevelopmental disorders may show patterns of symptoms that are distributed across the boundaries of autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) and are associated with significant disturbances in several domains of functioning, including affect regulation, social behaviour and interaction, as well as thought processes. Two constructs have emerged in the study and description of those children: The multidimensionally impaired syndrome and multiple complex developmental disorder (MCDD) (Werry 1992, Masi 2006, Cochran 2013, Driver 2013). However, these diagnoses are not included in the most common diagnostic classification systems (currently Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) and International Classification of Diseases -10 (ICD-10)). Furthermore, on the other end of the psychosis continuum, an estimated median of 10-17% of the general population of children and adolescents report non-clinical psychotic symptoms, such as hallucinations and delusions (Jeppesen 2014, Kelleher 2012).

In recent years, there has been considerable interest in early identification of psychosis in children and adolescents (Okkels 2012, Schimmelmann 2013, NICE guidelines 2013). Early identification after onset of psychosis aims to reduce the duration of untreated psychosis (DUP), i.e., the time from onset of psychotic symptoms to initiation of adequate treatment. The early detection and treatment of people at risk for and in the earliest phases of psychotic disorders is currently regarded as the most promising strategy to reduce the consequences of full-blown psychotic disorder in the population by improvement of treatment-outcome and long-term prognosis (Marshall 2005, Melle 2008). Longer DUPs have been found among EOS patients compared to AOP patients (Schimmelmann 2013), and for this reason a focus on reducing DUP might be even more important in EOP than in AOP patients. Several explanations of why children and adolescents may have a higher risk of delayed identification have been offered (Schimmelmann 2013). Positive symptoms may be overlooked in these patients and seen as an adolescent crisis. Moreover, comorbid conditions (substance abuse, developmental disorders, etc) may mask the emergence of a psychotic disorder. Also, the possibly greater frequency of an insidious onset of psychosis in these patients makes it more difficult to recognize the psychotic symptoms initially. Furthermore, health professionals may, partly because of the rarity of the disorder in childhood and early adolescence, not be sufficiently trained to assess psychotic symptomatology in children and adolescents, and

health professionals may hesitate to make a diagnosis of schizophrenia in a child or adolescent. In addition, compared to adults, considerable resources are often invested in helping psychiatrically ill youths, e.g., symptoms may be treated on a more general level, postponing the diagnosis until obvious psychotic symptoms combined with functional deficits become manifest. On the other hand, diagnosis of early states of the disorder may increase risk of misclassification, especially among children and adolescents, leading to an increased risk of stigmatization and potentially unnecessary treatment with antipsychotics.

Meta-analyses of a large number of studies in adults demonstrate that shorter DUPs correlate with a better course and outcome of schizophrenia-spectrum psychosis (Marshall 2005, Perkins 2005). DUP is strongly related to negative symptoms (Boonstra 2012), and the literature suggests that longer DUPs may reduce the treatment responsiveness of negative symptoms, and that efforts to shorten DUP might decrease negative symptom severity and lead to a better outcome (Melle 2008). However, not only are negative symptoms by nature a barrier for seeking help, but these deficit phenomena are also generally difficult to treat effectively. Recent studies have shown that negative symptoms could play a central role in inhibiting the process of recovery from schizophrenia and in worsening the long-term prognosis of the disease (Strauss 2010, Austin 2013).

Knowledge about the clinical presentation and phenomenology of psychosis in childhood and adolescence is the first step towards identifying improved strategies for early detection and development of more operational treatment guidelines. Currently, the commonly cited knowledge is based on a small number of studies of limited quality due to small sample sizes, retrospectively defined samples, lack of standardized assessments for diagnostic evaluation, and the mixing of data from first- and multi-episode patients. In order to provide high-quality evidence and compare this against the currently held notions, we systematically reviewed the literature on the phenomenology and outcome of first-episode non-affective psychosis in children and adolescents, published since 1990. We chose 1990 as the starting point to include only studies using either ICD-9/ICD-10 or DSM-IV criteria for schizophrenia. The specific aims of the current study of predominantly non-affective psychosis in children and adolescents were to: 1) Describe the demographic, illness and treatment characteristics; 2) Determine the illness trajectories, including diagnostic stability and symptomatic and functional outcomes; and 3) Explore correlates and predictors of severity and outcome of illness in the first years after treatment initiation.

Methods

Search

We searched the databases PubMed, PsycInfo and EMBASE and hand-searched reference lists of eligible papers and pertinent reviews for studies published since January 1st, 1990 reporting non-retrospective data in children or adolescents with a diagnosis of predominantly non-affective psychosis using the following search criteria:

PubMed:"Schizophrenia"[Mesh] OR schizophren* **AND** child[MeSH Terms] OR child, preschool[MeSH Terms] OR child* OR child OR adolescent[MeSH Terms] OR adolescen* OR youth OR adolescent **AND** "thought disorder" OR thought dis* OR psychos* OR psychotic disorders[MeSH Terms] OR schizophrenia and disorders with psychotic features[MeSH Terms] OR (psychot*OR "psychotic disorder" OR paranoid disorders[MeSH Terms] OR "paranoid disorder" OR paranoi* OR hallucinations[MeSH Terms] OR hallucination OR hallucinat* OR delus* OR delusion OR delusions[MeSH Terms]) OR phenomenology* **AND** "first episode" OR "recent onset" OR "early onset" OR "early detection" OR "early diagnosis" OR early diagnosis[MeSH Terms] OR schizophrenia, childhood[MeSH Terms] OR "early onset schizophrenia" OR "adolescent onset schizophrenia" OR "childhood onset schizophrenia" OR "early onset psychosis" OR "childhood onset psychosis" OR "adolescent onset psychosis" **AND** treatment outcome[MeSH Terms] OR outcome assessment[MeSH Terms] OR outcome* OR "diagnostic stability" OR course*

EMBASE: exp schizophrenia OR schizophren*.mp. AND exp child OR youth.mp. OR adolescen*.mp. OR child*.mp. OR exp juvenile AND "first episode".mp. OR "recent onset".mp. OR "early onset".mp. OR "early detection".mp. OR "early diagnosis".mp. OR early diagnosis OR "early onset schizophrenia".mp. OR "childhood onset schizophrenia".mp. OR "adolescent onset schizophrenia".mp. OR "early onset psychosis".mp. OR "childhood onset psychosis".mp. OR "adolescent onset psychosis".mp. AND exp treatment outcome OR exp outcome assessment OR outcome*.mp. OR "diagnostic stability".mp. OR course*.mp. AND exp psychosis OR hallucinat*.mp. OR delus*.mp. OR phenomenology*.mp. OR paranoi*.mp. OR thought dis*.mp. OR psychos*.mp. OR psychot*.mp. OR "psychotic disorder".mp.

PsycInfo:exp schizophrenia OR schizophren*.mp. **AND** child*.mp. OR adolescent*.mp. OR youth.mp. **AND** outcome*.mp. OR course*.mp. OR "diagnostic stability".mp. OR exp treatment

outcomes OR outcome assessment.mp. **AND** "childhood onset psychosis".mp. OR "childhood onset schizophrenia".mp. OR "adolescent onset psychosis".mp. OR "early onset psychosis".mp. OR "early onset schizophrenia".mp. "childhood onset schizophrenia".mp. OR "adolescent onset schizophrenia".mp. OR "first episode".mp. OR "recent onset".mp. OR "early onset".mp. OR "early detection".mp. OR "early diagnosis".mp. **AND** "thought disorder".mp. OR thought dis*.mp. OR psychos*.mp. OR psychot*.mp. OR "psychotic disorder".mp. OR "paranoid disorder".mp. OR paranoi*.mp. OR hallucination.mp. OR delusion.mp.OR hallucinat*.mp. OR delus*.mp. OR phenomenology*.mp. OR exp psychosis OR exp perceptual disturbances OR exp thought disturbance

The last search was performed on August 7th 2014.

Inclusion and Exclusion Criteria:

To be included, the studies had to fulfill the following criteria:

a) At least 50% of the participants suffered from non-affective psychosis (first- or multi-episode)

b) Mean age of participants below 19 years at baseline

c) Clinical samples recruited through mental health services

d) Cross-sectional or prospective design

e) Data in at least 20 participants at baseline

f) Standardized, validated instruments used for diagnostic evaluation and psychopathological examination

g) Studies should report count data, proportions or scores of psychotic symptoms (e.g., hallucinations, delusions, thought disorder, bizarre behaviour, catatonia) or continuous data on psychopathology

h) No study restriction for inclusion based on a threshold for psychopathology scores

i) Publications in English language

Studies were excluded according to the following criteria:

a) Patients suffering from psychotic disorders that were clearly related to substance abuse or physical conditions.

b) Retrospective design

c) Review articles

As indicated above, we decided to include only studies with a prospective or cross-sectional design and of clinical cohorts with research assessments using standardised psychometric instruments. This was to minimize ascertainment biases and imprecisions of recording in retrospective evaluations of diagnoses and psychopathology as well as selection biases from unmeasured attrition during follow-up.

Extracted Variables:

From each study we extracted detailed data on study population (first-episode psychosis or mixed first-episode and multi-episode patients), sampling years, number of patients at baseline and follow-up, mean age at baseline, mean age at onset of psychosis, follow-up time, percent of males, psychiatric family history, diagnostic instrument used, diagnoses, diagnostic stability, treatment characteristics, psychometric instruments used, measures of positive psychotic symptoms, negative psychotic symptoms, symptoms of disorganization, affective symptoms, and general/other psychopathology, instruments for measuring social, premorbid and global function, DUP, duration of untreated illness (DUI), measures of social function, premorbid function/developmental delay, co-morbidity, and IQ.

Statistical Analyses

We used descriptive statistics to summarize the study-, patient and illness characteristics of the included papers, reporting weighted means ± SD and weighted proportions. In longitudinal studies, we compared baseline psychopathology scores with endpoint ratings, using paired t-tests to assess if changes were significant over time. The following variables with at least 3 studies contributing data were examined: Positive and Negative Syndrome Scale (PANSS, Kay et al. 1987) total score, PANSS positive and negative symptom sub-scores, Clinical Global Impressions-Severity (CGI-S

scale, Guy 1976) scores, Children's Global Assessment Scale (CGAS, Shaffer 1983)/Global Assessment of Functioning (GAF, Endicott 1976) scores.

Furthermore, we conducted exploratory correlational analyses testing the associations between each of the following baseline variables, using the reported means per study as the unit of analysis: first vs. mixed first-and multi-episode sample, % males, age, age at illness onset, IQ, duration of untreated psychosis (DUP), % with presence of any psychiatric family history, % primary diagnosis of schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified (psychosis-NOS), schizophrenia-spectrum disorders, bipolar disorder and depressive disorder, as well as baseline scores in PANSS total score, PANSS positive, negative and general psychopathology symptom sub-scores, CGI-S scores and GAF/CGAS scores. For exploratory analyses of factors influencing the change in psychopathology scores, all baseline variables were examined as potential moderators and study duration and attrition were examined as potential mediating factors. Since most variables were non-normally distributed, we used non-parametric tests, i.e., Kruskall Wallis test for comparison of continuous variables across 2 categorical groups (i.e., first episode vs mixed samples) and Spearman's rho for all other analyses testing correlations between two continuous variables. All analyses were conducted in JMP 5.0.1, SAS Institute, Inc, 1989-2003, Cary, North Carolina), using two sided tests with alpha set at 0.05.

Results:

Study characteristics

The literature search resulted in 1186 hits after duplicates were removed (figure 1). An additional 17 publications were identified through hand search of reference lists; thus, a total of 1203 records were screened. 399 records were excluded based on title, 609 were excluded based on abstract, and the remaining 195 full text articles were assessed for eligibility. Altogether, 160 of these full text articles were excluded due to mean age of participants above 19 years (N=90), review paper (N=24), retrospective design (N=23), <20 participants (N=7), <50% with non-affective psychosis in the study (N=6), no psychopathology scores (N=4), sample at risk of psychosis (N=4) or sample selected for severe illness (N=2).

Study, patient and treatment characteristics (tables 1, 2 and 3)

The 35 included studies represented 28 independent samples, of which 22 were prospective and 6 were cross-sectional, with a total of 1506 patients at baseline and 773 patients at follow-up (after a mean of 2.2 years). The studies used a range of psychometric and diagnostic instruments (table 1).

Seventeen samples included only first-episode patients (n=872) and eleven samples included a mixture of first- and multi-episode/chronic patients (n=634) (table 1).

The mean age of patients was 15.6±1.9 years at baseline (range of means: 9.6-18.4 years) and the mean age at onset of psychosis was 14.5±2.4 years (range of means 7.7-16.4 years) (table 2). The mean DUP was 17.2±12.8 months (range of means 2-45 months). The mean percentage of males was 62.3±10.8%.

At baseline, 89.0% of the patients had a diagnosis of a schizophrenia-spectrum psychosis (table 2). Co-morbid psychiatric disorders were common. These included primarily posttraumatic stress disorder (PTSD: 34.3%), attention-deficit/hyperactivity disorder (ADHD) and disruptive behaviour disorders (oppositional defiant disorder (ODD) and conduct disorder (CD)) (together: 33.5%), substance abuse disorder (32.0%) and,while a co-morbid diagnosis of pervasive developmental disorder (PDD) was found in only 12.5% of the patients (table 2).

More than 90% of the patients were treated with antipsychotic medications at baseline (table 3). Co-medications, primarily antidepressants and mood stabilizers, were common.

Phenomenology at baseline and diagnostic stability (table 4)

The most frequently recorded symptoms were auditory hallucinations (81.9%; any: 70.3%, other: 54.8%), followed by delusions (any 77.5%, persecutory 48.5%, referential 35.1%, grandiose 25.5%) (table 4).

Thought disorder was common (65.5%), and 52.8% of patients were reported to display bizarre behaviour. A total of 50.4% had negative symptoms and 52.3% had flat/blunted affect. Data on affective symptoms were limited.

Diagnostic stability (table 5)

Nine studies reported both baseline and a follow-up diagnoses. In these studies, 88% of the patients at baseline and 75% at follow-up had a diagnosis of a schizophrenia-spectrum disorders, whereas the proportion of patients with affective disorders increased (12.2% to 24.5%) (table 5). Overall, the proportion of patients with fully developed syndromes of schizophrenia (31.9% to 40.2%), bipolar disorder (8.9% to 14.3%) or depressive disorder increased, and proportions of patients with psychosis NOS (15.8% to 12.0%) and, especially, schizophreniform disorder (21.3% to 1.1%) decreased, but due to the small samples diagnostic shifts were not significant.

Psychopathology at baseline and over time (table 6)

Mean PANSS total, positive and negative symptom scores at baseline were 84.3±10.9, 19.3±4.4 and 20.8±2.9 at baseline. Mean baseline CGI-S score was 5.0±0.7 and CGAS/GAF scores were 35.5±9.1 (table 6)

In prospective studies with both baseline and follow-up data, all psychopathology ratings improved significantly from baseline to follow-up. In these studies, PANSS total, positive and negative symptom scores were 84.5±10.8, 19.4±4.4 and 20.2±2.9 respectively at baseline, and 60.8±6.1 (p=0.0006, N=7), 12.4±2.0 (p=0.0004, N=10) and 16.6±2.4 (p=0.0003, N=10) at follow-up. CGI-S scores reduced from 5.5±0.1 at baseline to 3.2±0.2 at follow-up (p=0.012, N=4), and CGAS/GAF scores increased from 38.4±10.1 to 63.8±9.0 (p=0.0046, N=6).

Direct, post hoc comparison between youth and adults (table 7)

Six studies, representing 5 samples, directly compared the phenomenology of early-onset (EOP) and adult onset psychosis (AOP). The mean age at baseline was 17.6±0.7 years in EOP and 23.9±4.1 years in AOP patients. The mean age at onset of psychosis was 16.2±0.3 and 23.5±1.7 years, respectively. The percentage of patients with schizophrenia-spectrum disorders was 90±5.9% in the EOP patients and 85±10.5% in the AOP groups.

The percentage of males was only slightly lower in EOP compared to AOP patients (63.1±9.9 % vs. 69.2±6.4%,p=0.28), and baseline CGAS/GAF scores were similar in both groups (28.9±5.2 vs. 29.6±5.3, p=0.88. However, more EOP patients had schizophrenia-spectrum disorders (90.0% vs. 85.0%, p=0.036) and the DUP was almost 3.5 times longer in EOP than in AOP patients (18.7±6.2 months vs. 5.4±3.1 months, p=0.0027).

Baseline predictors of outcomes (table 8)

Table 8 summarizes the baseline predictors of outcomes after 1-4 years of follow-up as reported by individual studies. More positive and negative symptoms at baseline significantly predicted a worse illness severity at follow-up. Less negative symptoms at baseline significantly predicted remission and a better social functioning at follow-up, and less positive symptoms at baseline significantly predicted a better quality of life after 1-4 years.

A better premorbid adjustment significantly predicted remission, and more favourable outcomes on global function, social function and quality of life at follow-up, whereas worse premorbid adjustment significantly predicted more negative symptoms and worse illness severity at follow-up.

Exploratory correlational analyses of associations between diagnosis, age at onset of illness, severity and change of psychopathology and global functioning

Age at illness onset and at baseline:

First-episode vs. mixed first-/multiepisode samples had a higher mean age at onset (N=10, 15.2 ± 0.9 vs. N=7, 11.5 ± 2.4, r^2=0.541, p=0.0013) and a higher mean age at baseline (N=15, 16.0 ± 2.0 vs N=10, 14.7 ± 1.6, r^2=0.106, p=0.026). A higher baseline PANSS total score was associated with higher age at illness onset (rho=1.0, p<0.0001). Psychosis NOS and affective disorders diagnosed at entry into the study were associated with a lower mean age at onset (both rho= -1.0, p<0.0001), as well as a lower mean age at baseline (psychosis NOS: rho= -0.857, p=0.0065; affective psychosis: rho= -1.0, p<0.0001). By contrast, a diagnosis of schizoaffective disorder (rho=0.538, p=0.0472) or schizophreniform disorder (rho= 0.682, p=0.0103) were associated with a higher age at onset.

DUP

First-episode vs. mixed samples was marginally associated with a shorter DUP (N=9, 10.9±8.4 vs. N=3, 32.1±13.8, r^2=0.516, p=0.052).

Baseline Psychopathology:

A higher baseline PANSS total sub-score was associated with a higher baseline PANSS positive (rho=1.0, p<0.0001) and PANSS general (rho=0.9, p=0.0374), but not PANSS negative sub-score (rho=0.476, P=0.233). Male sex (N=27) was marginally associated with higher baseline PANSS-total (p=0.072) and PANSS-positive symptom scores (p=0.057). A diagnosis of affective psychosis was associated with a higher GAF/CGAS score at baseline (rho= 1.0, p<0.0001).

Change in Psychopathology:

A greater PANSS total score improvement (decrease) was associated with higher baseline PANSS total score (rho= -0.857, p=0.0137) and PANSS positive sub-score (rho= -0.857, p=0.0137) as well as with a greater PANSS positive sub-score reduction (rho=0.964, p=0.0005).

Greater PANSS positive sub-score improvement (decrease) was associated with higher baseline PANSS total scores (rho= -0.929, p=0.0025) and all PANSS sub-scores (PANSS positive: rho= -0.9329, p<0.0001, PANSS negative: rho= -0.685, p=0.0289, PANSS general: rho= -0.829, p=0.0416). Greater PANSS negative sub-score improvement (decrease) was correlated with a higher baseline PANSS negative sub-score (rho= -0.721, p=0.0186) and greater PANSS positive sub-score reduction (rho=0.697, p=0.0251). Moreover, a diagnosis of schizophrenia was significantly associated with less PANSS negative sub-score reduction (rho=0.943, p=0.0048).

Greater CGI-S score improvement was associated with a higher baseline CGI-S score (rho= -1, p<0.0001). Greater improvements in global functioning (CGAS/GAF) scores were associated with shorter DUP (rho=1.0, p<0.0001) and a greater improvement (decrease) in PANSS positive (rho= -1, p<0.0001) and PANSS negative sub-scores (rho= -1, p<0.0001).

Discussion:

In the current review that included 35 papers representing 28 samples of youth with early onset, predominantly non-affective psychosis (89.0%), the analysed samples had a mean age of 15.6 years at baseline, a mean age at illness onset of 14.5 years, and 62.3% were male. The main findings of this systematic review include: 1) youth were moderately to markedly ill, with similar levels of positive and negative symptoms at baseline; 2) Hallucinations (70.3%), predominantly auditory (81.9%), and delusions (77.5%) were very common, followed by thought disorders (65.5%),

bizarre/disorganized behaviour (52.8%) and flat or blunted affect/negative symptoms (52.3%/50.4%); 3) The rate of co-morbidity was high; 4) All psychopathology scores improved significantly during a mean follow-up of 2.2 years, with less improvement and higher levels of residual negative symptoms; 5) Schizophrenia was correlated to less improvement in negative symptoms; 6) PANSS positive and negative symptoms scores and changes were inter-correlated, and PANSS total score and change were correlated to PANSS positive and general, but not to negative subscale scores;7) The proportion of patients with fully developed syndromes of schizophrenia, bipolar disorder or depressive disorder increased, while psychosis NOS and, especially, schizophreniform disorder decreased, but diagnostic shifts were not significant, likely due to small samples; 8). DUP was significantly longer in EOP compared to AOP, and in EOP longer DUP was significantly correlated with less improvement in global functioning.

The preponderance of males (62%) is in accordance with an Australian study of first episode psychosis, 1997-2000 (EPPIC) that reported an overall male percentage of 65% (Amminger 2006) and a meta-analysis that found a rate ratio for males:females of 1.4:1 (McGrath 2008). A Danish register-based study of the incidence of early onset psychosis from 1971-2010 (Okkels 2012), reported an overall male percentage of 54%, with a male percentage of 65% in the earlier time period 1971-1993, but an equal gender distribution in the later period 1994-2010. The study by Okkels et al. (2012) indicates a possible historical shift toward a more equal male:female ratio among adolescents with EOS, as compared to the older EOS samples. As no larger epidemiological studies are available for comparison in this area, our finding of male preponderance across analyses of samples published 1990-2014 may possibly reflect sample selection, unless the Danish finding by Okkels et al. reflects a local phenomenon. The mean age at baseline in our sample (15.6 years) is similar to the one found by Okkels et al. (15.8 years at first diagnosis).

The EOP patients in the included cohorts were moderately to markedly ill at baseline and had serious problems in global functioning. The mean CGI-S was 5.0, “markedly ill”, and the mean PANSS total score was 84 (corresponding to “moderately” to “markedly ill” on the CGI-S scale according to the interpretation of the PANSS by Leucht and colleagues (Leucht 2005)). The mean GAF/CGAS score at baseline was only 34, meaning that these patients were seriously functionally impaired. Affective psychosis was associated with higher CGAS/GAF scores at baseline, probably due to less negative symptoms (social withdrawal) in this patient group. A longer DUP was

significantly associated with less CGAS/GAF improvement, emphasizing the importance of an early recognition of psychotic illness in order to improve long-term prognosis (Hill 2012, Chang 2012, Correll 2010).

Our data on specific psychotic symptoms confirmed the general understanding that hallucinations in EOP patients are mostly auditory in nature. Hallucinations of any kind were reported in 70% of the patients, auditory hallucinations in 82%, and delusions (primarily persecutory) in 77%. The overall frequency of hallucinations is slightly lower compared to that reported in a study of Biederman et al. (Biederman 2004) who found 85% of youth with broadly defined psychosis to have hallucinations. The authors also found higher percentages for each subtype than we found in the included cohorts in this review. The distribution of hallucination types found by Biederman et al. (2004) is in line with findings in studies, which included more narrowly defined early onset schizophrenia (Kolvin 1971, Green 1984, Russel 1989). The frequency of delusions identified in our review was higher compared to older EOP studies, which reported delusions in 54-63% of youth (Kolvin 1971, Green 1984, Biederman 2004, Russel 1989). We found a predominance of delusions of persecution and reference, similar to the finding in a study in adults with first-episode schizophrenic psychosis (Ellersgaard 2013). Patients with EOP are thought to have more disorganization and more formal thought disorder than AOP patients (Häfner 1995). We found that 65% of patients with EOP had formal thought disorder and 36% had disorganized/pressured speech. The frequency of formal thought disorder was close to the frequency reported by other studies on more narrowly defined EOS (Russel 1989, Kolvin 1971), while one study found 100% of the patients had formal thought disorder (Green 1984).

The rate of co-morbidity was high, and a total of 32% of patients had a substance abuse disorder. In the studies comparing first-episode EOP and AOP patients, co-morbid drug substance abuse was reported in almost 50% of EOP and 60% of AOP patients. Substance abuse in adolescents remains a problem. A study from the U.S. found that substance abuse admissions represented 1.25% of adolescent admissions to acute care hospitals, and that 50% of these patients had a comorbid mental health diagnosis (Chisolm 2006). Substance use may influence the onset and course of psychosis, and ongoing substance use is associated with negative outcomes (Sara 2014, Bertelsen 2009). Studies have suggested that age at onset of psychosis might be lower in patients with cannabis use disorder, indicating that cannabis might exert an indirect adverse effect on brain maturation

resulting in an earlier age at onset of psychosis (Schimmelmann 2011, Large 2011, Stefanis 2013). In a randomized clinical trial with adults suffering from first-episode schizophrenia spectrum psychosis, 27% had substance abuse (Petersen 2007), whereas another study in first-episode adolescent patients found baseline cannabis use disorder in 53% of the patients (Schimmelmann 2012). These results suggests that among patients with a psychotic illness the percentage of patients with substance abuse is high, but probably varies substantially between different samples (partly due to different study in- and exclusion criteria). A high level of reported co-morbid diagnoses was also reported in other studies of children and adolescents with schizophrenia (Driver 2013, Ross 2006). A total of 99% of childhood-onset patietns in the study by Ross et al. (2006) had at least one lifetime comorbid axis 1 disorder (according to DSM-IV diagnostic criteria). The most common co-morbid disorder in their sample was ADHD (84%), whereas a history of trauma was rare. The high level of PTSD diagnoses (34%) in the current sample supports the notion that trauma play a role in the pathogenesis of EOS as well as psychotic symptoms in general and in bipolar disorder (Dvir 2013, Harley 2010, Varese 2012, Li 2014, Aas 2014). A review of cohort and cross-sectional studies found significant associations between adversities in childhood and psychosis and indicated that patients with psychosis were 2.72 times more likely to have been exposed to childhood adversities than healthy controls (Varese 2012). In a study of first episode patients with psychotic mania, 48% of patients reported direct personal traumatic experiences prior to the onset of psychosis (Daglas 2014), and patients with past trauma had significantly poorer social and occupational function at the 12-month assessment.

All mean psychopathology and global functioning ratings improved significantly over time. EOP is generally thought to have a poorer prognosis than adult onset disorder (Remschmidt 2012), but recent studies from early intervention services suggest that early-onset patients might have an equally good or even better outcome than adult-onset patients (Amminger 2011, Schimmelmann 2007), at least in settings with comprehensive early recognition and outreach efforts (Schimmelmann 2013). However, these services and studies do not include children, but only adoelscents aged 15 and above. Thus, the generalization to EOP samples with prepubertal patients in whom psychosis interrupts maturation and developmental processes very early is unclear. Nevertheless, additional studies are needed to clarify if a greater focus on EOP and better treatment options in the recent years may have led to a higher frequency and earlier detection, better treatment response and recovery, translating into a better prognosis than before. In this context, it is also

possible that the earlier reluctance towards making a schizophrenia diagnosis restricted the population of EOS patients to those with a more severe disorder and a worse outcome. A recent review of long-term outcomes in youth with schizophrenia found converging evidence (Clemmensen et al. 2012). In aggregated data analyses in this systematic review, poorer outcome of individuals with EOS were associated with longer follow-up periods, male sex, as well as with patients having been diagnosed before 1970 (Clemmensen et al. 2012). However, without a direct comparison of change and endpoint scores across samples identified and treated at different times, conclusions have to be cautious. Therefore, additional studies are needed to clarify if a greater focus on EOP and better treatment options in the recent years may have led to a higher frequency and earlier detection, better treatment response and recovery, translating into a better prognosis than before.

Negative symptoms were present in half of the patients, and the level of negative symptoms was moderate at baseline (mean PANSS negative subscore: 21) with less reduction at follow-up, compared to the positive symptoms. The included studies found that more negative symptoms at baseline significantly predicted a worse illness severity at follow-up, whereas less negative symptoms significantly predicted remission and a better social function. We found that a diagnosis of schizophrenia was significantly associated with less PANSS negative sub-score reduction. These findings are consistent with results from adult studies (Fenton 1991; Moeller 2010; Foussias 2010; Carbon and Correll – in press). The prevalence of clinically relevant negative symptoms is estimated at approximately 15% in first-episode patients and 25-30% in chronic schizophrenia (Foussias 2010). Baseline data from the large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed prominent negative symptoms in 40% of participants with chronic schizophrenia (Rabinowitz et al. 2013). One half of this subgroup showed prominent negative symptoms without prominent positive symptoms, and the other half showed prominent negative symptoms plus prominent positive symptoms. Compared to these percentages in AOP patients, we found higher proportions of EOP patients with negative symptoms (50-52%), indicating a possible reason for EOS patients to have the potential for poor outcomes, especially since negative symptom levels remained higher than positive symptom levels at follow up.

The percentage of patients with a diagnosis of schizophrenia was higher at baseline than at follow-up, whereas the opposite was the case in patients with an affective disorder. These data may reflect

that in EOP a diagnostic shift (although it did not reach statistical significance) is primarily from schizophrenia spectrum disorders to affective disorders. A review of COS patients reported that approximately 30-50% of patients with affective or atypical psychotic symptoms were misdiagnosed as COS (Driver 2013). Moreover, a large-scale follow-up study of first-episode psychosis patients found that the change from non-affective psychosis to affective psychosis was much more common than vice versa (Salvatore 2009). On the contrary, another study in first-episode patients found the predominant pattern of diagnostic shift was towards schizophrenia spectrum disorder (Chang 2009). Chang et al. (2009) found that a family history of psychosis and a longer DUP were associated with diagnostic transition towards schizophrenia spectrum disorders. In line with these findings, another study in patients with first-episode psychosis identified female gender, a shorter DUP and a higher level of premorbid function as predictive factors for a diagnostic shift from non-affective psychosis to bipolar disorder (Kim 2011).

Patients with affective psychosis or psychosis NOS had a lower age of illness onset and at baseline, whereas patients with schizophreniform disorder or schizoaffective disorder had a higher age at onset. Regarding schizophreniform disorder, these results are somewhat surprising, since the less well-defined diagnoses might be expected to be more common in the younger patients, as these diagnoses are the least stable (Chang 2009, Salvatore 2009). Nevertheless, our results might be explained by differences in the selection and diagnostic classification across the different samples.

In prior studies, DUP is generally reported to be longer in EOP than in AOP patients (Schimmelmann 2013). The mean DUP across all included samples with information was 17.2 months (range 2-45 months). In five studies directly comparing EOP and AOP patients, EOP patients had a significantly longer DUP than AOP patients (18.7±6.2 months vs. 5.4±3.1 months), although the difference between EOP and AOP patients varied across studies. A review of 28 studies of adult patients with first-episode psychosis reported a much higher mean DUP of 14.2 months (61.4 weeks, Boonstra 2012) than in the studies that directly compared adults to youth, some of which included early recognition and outreach efforts. Nevertheless, even this longer DUP in adult studies in the literature was still, 3 months longer than the DUP reported across all EOS patients. However, the range of DUP found in other studies in EOP patients is somewhat longer (1-7 years, Russel 1989, Maziade 1996, Eggers 1997, Häfner 1995, Alaghband-Rad 1995) than the range reported in the included samples.

The results of the studies comparing EOP with AOP patients supported the findings in prior studies, in which EOP patients had more severe premorbid developmental and behavioural dysfunction compared to AOP patients (Schimmelmann 2007, Ballageer 2005, Joa 2009). The included studies found premorbid adjustment to be important since better premorbid adjustment was reported to significantly predict a higher frequency of remission, more favourable outcomes on global and social function and quality of life, whereas a worse premorbid adjustment significantly predicted more negative symptoms and a worse illness severity.

First-episode vs. more chronic samples had a higher mean age at onset, a higher mean age at baseline, less patients with psychosis-NOS, and a marginally shorter DUP. These results are likely explained by sampling selection, and probably do not reflect the natural history of how psychotic disorders unfold in children and adolescents. Childhood schizophrenia is rare, and small samples of patients with childhood-onset psychoses are likely to be very heterogeneous, including patients with less specific syndromes and longer DUP, while studies of first-episode samples often include adolescent patients who may be more easily diagnosed with a fully developed psychotic syndrome. The delay in diagnosis may be explained by the relative lack of specificity in the very early onset of psychosis, insidious onset, co-morbidities, reluctance towards deciding on a schizophrenia diagnosis, etc.

The results from this systematic review have to be interpreted within its limitations. Most importantly, the included studies were heterogeneous in design, sampling, assessments, duration of follow-up and the reporting of specific data. Moreover, both the number of studies and the corresponding number of patients contributing data for individual outcomes were quite limited in most cases and often did not provide sufficient data for inferential statistics. Overall, the generalizability of the results and the ability to identify reliable clinical correlates were reduced. Clearly, more detailed research in youth with early onset schizophrenia-spectrum disorders is needed, and data should be collected and reported as comprehensively as possible, using the reviewed outcomes as an example and minimum requirement.

Conclusion:

Phenomenological and symptomatic data in youth with schizophrenia-spectrum disorders are scarce. This review supports earlier findings of EOS patients suffering from substantial

impairments. Clinically significant levels of positive and negative symptoms were frequent, as were premorbid and/or co-morbid mental disorders. Symptoms and global functioning improved significantly over time, yet patients remained impaired on average and negative symptoms were less responsive than positive symptoms. Long-term studies are needed that identify best treatment strategies to improve outcome and functioning in youth with EOS.

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Table 1

Study/Sample Country (Sampling years)	Design Study population (F-E/mixed F-E + M-E)	Baseline n	Follow-up n (years)	Male sex,%	Mean age, baseline, years	Mean age, onset of psycho-sis	Psychometric instruments	Diagnostic instruments	Diagnoses n(%)
Calvo 2014 (Spain)	Prospective FE+ME	55	51 (0.75)	62	16.5		PANSS, CGAS	K-SADS-PL, DSM-IV	SZ-spectrum PSY=21(38.2) Non-AffPSY other=18(32.7) AffPSY=16(29.1)
Greenstein 2014 (Maryland, US)	Cross-sectional M-E	85		56	13,2	9,9	BPRS, SANS, SAPS, GAF, WISC/WAIS	SADS, DSM-IV	SZ=85(100)
Stentebjerg-Olesen 2013 (New York, US 2001-2007)	Prospective F-E+M-E	79	79	58	15.2		CGI-I, CGI-S, CGAS	DSM-IV	SZ=23(29.1) SA=2(2.5) Schizophreniform dis.=3(3.8) PsyNOS=50(63.3)

									Brief PSY=1(1.3)
TIPS (Langeveld 2012, Joa 2009) (Norway 1997-2001, 2002-2004)	Prospective F-E	43	33 (2)	51	17.1	15.6	PANSS, SCFS	SCID, DSM-IV	SZ=7(17) SA=12(28) Schizophreniform dis.= 5(12) PsyNOS=6(14) Brief PSY=5(12) Delusional dis.=2(5) AffPSY=6(14)
Remberk 2012 Poland (2005-2009)	Prospective F-E	32		47	16.7		PANSS, CGI-S,	Semistructured interview, ICD-10	SZ=24(75) Delusional dis.=1(3) Acute and transient PSY=3(9) Schizotypal dis.=4(13)
CAFEPS Sanchez-Gistau 2013 Castro-Fornieles 2011 Parellada 2011 Rapado-Castro 2010 Parellada 2009 Castro-Fornieles 2007	Prospective F-E	110	83 (2)	70	15.5	15.5	PANSS, CGI, YMRS, HDRS CGAS, GAF, PAS, WHO-DAS, SCOS, WISC-R/WAIS-III	K-SADS-PL, DSM-IV	SZ=44(40) SA=7(6) Schizophreniform dis.= 9(8) PsyNOS=16(15) Brief PSY=3(3)

Spain (2003-2005)									BD=22(20) DD=9(8)
Amminger 2011 EPPIC Australia (1998-2005)	Prospective F-E	41	41 (6.9)	66	16.5		BPRS-E, SANS, BDI, GAF, SOFAS	SCID, DSM-III-R/DSM-IV	SZ=20(48.8) SA=7(17.1) Schizophreniform dis.=11(26.8) PsyNOS=3(7.3)
Hassan 2011 Saudi Arabia (2003-2010)	Prospective F-E + M-E	37	37 (3.2)	61	17	12.2	PANSS, CGAS, PAS, CBS, GDS	K-SADS-PL, DSM-IV	Follow-up: SZ=30(81) PsyNOS=7(19)
David 2011 USA	Cross-sectional F-E + M-E	117		57	13.6	9.9	SAPS, SANS, CGAS		SZ=117(100)
Arango 2009 Spain	Prospective (Randomized open-label) F-E	50	32 (0.5)	78	16		PANSS, CGI-S, YMRS, HDRS, CGAS	K-SADS-PL, DSM-IV	SZ=17(34) BD=13(26) PSY-"other"=20(40)
Ledda 2009 Italy (1992-2002)	Prospective F-E	41	36 (5)	59	15.1	15.1	PANSS, BPRS, CGAS, GAF	K-SADS-PL, DSM-IV	Follow-up: SZ=17(41) SA=11(27) BD=13(32)

Fraguas 2008 Spain (2002-2003)	Prospective F-E	24	23 (2)	75	15.7	15.2	PANSS, GAF	K-SADS-PL, DSM-IV	SZ=4(16.7) SA=2(8.3) Schizophreniform dis+brief PSY.=4(16.7) PsyNOS=6(25) BD=7(29.2) DD=1(4.2)
Fulton 2008 Northern Ireland (2001-2004)	Prospective F-E	25		84		14.8	(K-SADS-PL), PAS	K-SADS-PL, DSM-IV	SZ=10(40) SA=2(8) Schizophreniform dis.=2(8) AffPSY=11(44)
Wozniak 2008 USA	Prospective F-E + M-E	36	14 (1)	64	14.6	14.6	PANSS, neurocogni-tive battery	K-SADS-PL, DSM-IV	SZ=14(39) SA=7(19) Schizophreniform dis.+brief PSY.=6(17) PsyNOS=9(25)
Schimmelmann 2007 EPPIC Australia (1998-2000)	Cross-sectional F-E	118	118	53	17.9	16.2	CGI-S, GAF, PAS	SCID, DSM-IV	SZ=4(39.3) SA=6(5.1) Schizophreniform dis.=38(32.5)

									BD=11(9.4) PSY-"other"=16(13.7)
Cervellione 2007 USA	Prospective F-E + M-E	26	(1.1)	58	16	13.1	BPRS, SANS, CGAS, PAS, neurocogni-tive battery	K-SADS-PL, DSM-IV	SZ=26(100)
Vyas 2007 UK	Prospective F-E	40	23 (4)	50	15.6	14.1	PANSS, GAF, PAS, SASS	SCID, DSM-IV	SZ=40(100)
Pagsberg 2008 Denmark	Cross-sectional F-E	29			15.7	13.6	SANS, SAPS, WISC-III/R, WAIS	PSE, ICD-10	SZ=15 (51.7) PsyNOS=5 (17.2) Delusional dis.=1 (3.5) Schizotypal dis.=6 (20.7 Acute/transient PSY=2 (6.9)
Meng 2006 Switzerland, Germany, Austria (1999-2002)	Prospective F-E	56	41 (1)	51	16.2		PANSS, CGI-S, SCS	SCID-I, DSM-IV	Follow-up: SZ=17(41.5) SA=2(4.9) Schizophreniform dis.= 4(9.8) PsyNOS=8(19.5) Brief PSY=4(9.8)

									Aff-PSY=6(14.6)
Pencer 2005 Canada	Prospective F-E	69	49 (2)	71	17.3		PANSS, CDSS, PAS, neurocogni-tive battery	SCID-I, DSM-IV	Follow-up: SZ=48(69.3) SA=1(1.5) Schizophreniform dis.=11(15.5) PsyNOS=5(7.7) PSY-"other"=4(6)
Muratori 2005 Italy	Prospective F-E	23		39	16.4	15.3	SANS, SAPS, CBCL, WISC-III-R	K-SADS-PL, DSM-III-R	SZ=23(100)
Ballageer 2005 PEPP Canada	Cross-sectional F-E	82		76	18.4	16.4	SANS, SAPS, CDS, GAF, PAS	SCID-I, DSM-IV	SZ-spectrum PSY=54(65.8) Non-AffPSY other=15(18.3) AffPSY=5(6.1) Substance inducedPSY=8(9.8)

Hlastala 2005 USA	Prospective F-E + M-E	69	39 (2)	68	14.8		BPRS, SANS, SAPS, DES, CGAS, WISC/WAIS	SCID, DSM-IV	SZ=27(39) Non-AffPSY other=20(29) BD=22(32)
Sporn 2004 USA	Prospective F-E + M-E	75		57			CGI, BPRS, SANS, SAPS, PAS, WISC-R/WAIS-R	K-SADS-PL, /DSM-IV	SZ=75(100)
Nicolson 2001 USA (1991-2001)	Prospective F-E + M-E	30	26 (4.1)	81	11.6	7.7	BPRS, CGI, SANS, SAPS, CGAS	K-SADS-PL, DSM-III-R/ DSM-IV	PsyNOS=30(100)
McClellan 1999, McClellan 1999b	Prospective F-E + M-E	55	30 (2)	64	14.8	13.2	SANS, SAPS, DES, CGAS, PAS	SCID, DSM-IV	SZ=18(33) SA=6(11) PsyNOS=15(27) BD=15(27) Organic PSY=1(2)
Asarnow 1994 USA	Prospective F-E	21	18	71			(K-SADS), CGAS, PAS	K-SADS-PL, DSM-III	SZ=21(100)
Green 1992 USA	Cross-sectional F-E	38		68	9.6		DSM-III (symptoms), CBI, WISC/WISC-R	DSM-III	SZ=38(100)

Total 28 samples	22 prospec-tive 6 cross-sectional 17 F-E 11 F-E + M-E	1506	773 (mean 2.2 years)	Mean 62.9	Mean 15.6	Mean 14.5	Number of samples: PANSS=16 CGI=10 BPRS=6 SANS/SAPS=12 YMRS=2 HDRS, CDS, CDSS=4 CGAS/GAF=18 WISC/WAIS=7 Neurocognitive battery=3 PAS=11 DES=2 SCS, SCSS, SCFS, SOFAS, SASS, SCOS, WHO-DAS, CBI or CBCL=7	Number of samples: ICD-10=2 DSM-IV=21 DSM-III(-R)=6 K-SADS-PL=17 SCID=10 PSE=1	Baseline: SZ=695 (53.3) SA=51(3.9) Schizophreniform dis.=74(5.7) PsyNOS=145(11.2) Delusional dis.=5(0.4) Schizotypal dis.=10(0.8) Acute/transient PSY=3(0.2) Brief PSY=9(0.7) Non-AffPSY other=168(12.9) BD=83(6.4) DD=9(0.7) AffPSY other=38(2.9) Organic PSY=1(0.1) Substance induced PSY=8(0.6)

AffPSY=affective psychosis, BD=bipolar disorder, BPRS=Brief Psychiatric Rating Scale, CBCL=Child behavior checklist, CBI=childrens behavioral inventory, CBS=Child Behavior Scale, CDS=Children´s Depression Scale, CDSS=Calgary Depression Rating Scale for Schizophrenia, CGAS=Childrens Global Assessment Scale, CGI(-S)=Clinical global impression scale (-severity), DD=depressive disorder, DES=Dissociative Experiences Scale, DSM=The Diagnostic and Statistical Manual of Mental Disorders, F-E=first-episode, GAF=Global Assessment of Functioning, GDS=General Developmental Scale , HDRS=Hamilton depression rating scale, ICD=International Classification of Diseases, K-SADS-PL= Kiddie Schedule for Affective disorders and schizophrenia – present and lifetime version, M-E=multi-episode, PANSS=positive and negative syndrome scale, PAS= Premorbid adjustment scale, PSE=Present State Examination, PsyNOS= psychosis not otherwise specified, SA=schizoaffective disorder, SANS=Schedule for negative symptoms, SAPS=Schedule for positive symptoms, SASS=Social Adaptation Self-evaluation Scale, SCID= Structured clinical interview for DSM disorders, SCFS= Strauss-Carpenter Level of Functioning Scale, SCOS=Strauss-Carpenter Outcomes scale, SCS=Strauss Carpenter Prognostic Scale, SOFAS=Social and Occupational Functioning Assessment Scale, SZ=schizophrenia, WAIS=Wechsler Adult Intelligence Scale, WHO-DAS=World Health Organisation-Disability Assessment Schedule, WISC=Wechsler Intelligence Scale for Children, YMRS=Young mania rating scale.

Table 2. Demographic and Illness Characteristics at study baseline

(means and proportions are weighted by the total number of patients in each study who contributed with a score)

Variable	Samples	Patients	Weighted Mean	Range
N, baseline	28	1506	51.9	21-118
N, last follow-up (6 months-7 years)	18	773	42.9	18-118
Attrition (proportion of baseline n lost at follow-up) %	17	895	22.5%	0-61%
Follow-up duration, mean	17	634	2.2 years	0.2-6.9 years
Age at baseline, mean	25	1385	15.6 years	9.6-18.4 years
Male, mean %	27	1477	62.3%	39-84%
Age at onset, mean	17	866	14.5 years	7.7-16.4 years
Duration of untreated psychosis	12	699	17.2 months	2.1-45.0 months
IQ, full scale	11	599	80.1	71.2-91.9
Psychiatric family history				
Any	5	253	41.3%	24.0-60.0%
Schizophrenia	4	184	32.1%	21.2-50.0%
Other than schizophrenia	5	229	28.1%	13.5-93.0%

Variable	Samples	Patients	Weighted Mean	Range
Schizophrenia spectrum psychosis, total n (%)	24	1303	**89.0%**	
Schizophrenia, n (%)	22	1191	53.3%	17-100%
Psychosis NOS, n (%)	9	497	11.2%	7-100%
Schizophreniform disorder, n (%)	8	493	5.7%	4-33%
Schizoaffective disorder, n (%)	10	572	3.9%	3-28%
Brief psychosis, n (%)	4	273	0.7%	1-12%
Schizotypal disorder, n (%)	2	61	0.8%	13-21%
Delusional disorder, n (%)	2	75	0.4%	3-5%
Acute and transient psychosis, n (%)	1	32	0.2%	9%
Other non-affective psychosis, n (%)	6	398	12.9%	3-66%
Affective psychosis, total n (%)	9	607	**10.0%**	
Bipolar disorder, n (%)	5	402	6.4%	9-32%
Depressive disorder, n (%)	1	110	0.7%	8%
Other affective psychosis, n (%)	4	205	2.9%	6-44%
Other Psychotic Disorders, total n (%)	2	137	**0.7%**	
Substance induced psychosis n (%)	1	82	0.6%	10%
Organic psychosis n (%)	1	55	0.1	2%
Co-morbidity				
ADHD-ODD-CD	5	299	33.5%	8-74%
Substance abuse	7	512	32.0%	13-68%
PTSD	2	80	34.3%	16-43%

Variable	Samples	Patients	Weighted Mean	Range
PDD	3	209	12.5%	4-25%

ADHD=attention deficit hyperactivity disorder; ODD=oppositional defiant disorder; CD=conduct disorder; PTSD=posttraumatic stress disorder; OCD=obsessive compulsive disorder; PDD=pervasive developmental disorder; Atypical AP= atypical antipsychotic

Table 3. Treatment Characteristics at Baseline and Follow-up

Variable	Samples	Patients	Weighted Mean	Range
Antipsychotic treatment				
Prebaseline	4	260	33.0%	24.0-62.0 %
Baseline	10	511	92.8%	54.0-100.0 %
Follow-up	4	187	81.7%	68.0-99.0 %
Co-medication				
Antidepressant, baseline	5	297	19.5%	15.0-36.0 %
Antidepressant, 1 year follow-up	3	108	19.4%	7.0-32.0 %
Mood stabilizer, baseline	5	288	24.3%	7.0-68.0 %
Mood stabilizer, 1 year follow-up	3	108	29.8%	10.0-54.0 %

Table 4. Specific Psychopathology: Psychotic Symptoms (Studies reporting on one symptom are not necessarily the same as those reporting on another symptom)

Specific Psychotic Symptom	Samples	Patients	Mean %	Range (%)
Hallucinations, any	4	120	70.3	55.6-90.0
Hallucinations, auditory	5	270	81.9	61.0-94.9
Hallucinations, visual/olfactory/other	5	270	54.8	4.0-80.3
Hallucinations, any, schizophrenia patient	3	161	81.3	59.0-89.0
Hallucinations, any, bipolar disorder patient	3	161	47.1	8.0-63.0
Delusions, any	4	120	77.5	62.9-92.0
Delusions, persecutory	3	132	48.5	42.1-56.0
Delusions, of reference	2	94	35.1	34.8-36.0
Delusions, grandiose	2	94	25.5	20.3-40.0
Delusions, other	2	107	31.7	29.0-36.8
Thought disorder	4	107	65.5	40.0-100.0
“Pressured/disorganized” speech	2	79	36.3	33.3-39.0
Bizarre behavior	4	181	52.8	20.0-76.5
Negative symptoms	2	74	50.4	37.0-80.0
Flat/blunted affect	2	107	52.3	52.0-52.4

Table 5. Primary diagnoses at baseline and follow-up in longitudinal studies with both a baseline and a follow-up diagnosis

Diagnosis	Longitudinal studies with a baseline and follow-up diagnosis		Baseline, longitudinal studies with both a baseline and a follow-up diagnosis	Follow-up, longitudinal studies with both a baseline and a follow-up diagnosis
	n, Samples	n, Patients		
Schizophrenia spectrum psychosis, total n (%)	**9**	**447**	**372 (88.0)**	**203 (75.2)**
Schizophrenia, n (%)	8	417	136 (31.9)	108 (40.2)
Psychosis NOS, n (%)	5	248	67 (15.8)	32 (12.0)
Schizophreniform disorder, n (%)	6	345	91 (21.3)	3 (1.1)
Schizoaffective disorder, n (%)	7	396	46 (10.8)	37 (13.8)
Brief psychosis, n (%)	2	126	10 (2.4)	1 (0.2)
Delusional disorder, n (%)	1	43	2 (0.5)	0 (0)
Other non-affective psychosis, n (%)	2	142	20 (4.7)	21 (7.8)
Affective psychosis, total n (%)	**3**	**252**	**52 (12.2)**	**66 (24.5)**
Bipolar disorder, n (%)	3	252	38 (8.9)	38 (14.3)
Depressive disorder, n (%)	1	83	8 (1.9)	11 (4.1)
Other affective psychosis, n (%)	2	126	6 (1.4)	17 (6.2)
Organic psychosis n (%)	1	51	1 (0.2)	1 (0.4)

Table 6. Psychopathology ratings at Baseline and Over Time

	Baseline (All Studies with Data)				Baseline (Studies with Follow-up Data)				Follow-up (Studies with Follow-up Data)				Baseline vs Follow up
Rating Scale	**Mean ± SD**	**Range**	**N, Samples**	**n, Patients**	**Mean ± SD**	**Range**	**N, Samples**	**n, Patients**	**Mean ± SD**	**Range**	**N, Samples**	**n, Patients**	**p- value**
CGI–Severity	5.0±0.7	4.2-5.6	7	467	5.5±0.1	4.3-5.6	4	283	3.2±0.2	2.9-3.3	4	233*	**0.012**
Global function (GAF/CGAS)	35.5±9.1	21.6-61.4	13	875	38.4±10.1	21.6-61.4	6	349	63.8±9.0	49.1-75.7	6	308*	**0.0046**
PANSS total	84.5±10.9	65.4-99	8	392	84.5±10.8	65.4-99.0	7	363	60.8±6.1	56.8-69.3	7	250*	**0.0006**
PANSS positive	19.3±4.4	13.8-26.8	11	544	19.4±4.4	13.8-26.8	10	515*	12.4±2.0	11.3-15.6	10	355*	**0.0004**
PANSS negative	20.8±2.9	16.6-24.5	11	544	20.2±2.9	16.6-24.5	10	515*	16.6±2.4	14.4-20.8	10	355*	**0.0003**
PANSS general	41.6±8.1	27.5-49.7	6	312	42.4±7.3	27.5-49.7	6	312*	30.8±2.7	28.8-35.3	6	208*	**0.044**

CGAS=Children's Global Assessment Scale; CGI= Clinical Global Impressions Scale; GAF=Global Assessment of Function Scale; BPRS=Brief Psychiatric Rating Scale; PANSS= Positive and Negative Syndrome Scale

*** One study did not report the overall nBolded values indicate p<0.05**

Table 7. Samples with early onset and adult onset psychosis patients (Amminger 2011, Langeveld 2012, Schimmelmann 2007, Pencer 2005, Ballageer 2005):

	Early onset psychosis patient (5 samples, n=353)		**Adult onset psychosis patients (5 samples, n=1220)**		**n, Patients: youth/adults**
	Weighted Mean	Range	Weighted Mean	Range	
Age at onset, years	16.2	15.6-16.4	23.5	22.5-26.4	243/826
Age at baseline, years	17.6	16.5-18.4	23.9	22.6-33.8	353/1220
Male %	63.1±9.9	51-76	69.2±6.4	58-76	353/1220
DUP, months	18.7±6.2	8.9-24	5.4±3.1	2-10.7	166/1151
Primary diagnosis					
Schizophrenia spectrum psychosis, total n (%)	255 (89.8)		978 (85.0)		284/1151
Schizophrenia, n (%)	74 (26.0)	17-48.8%	310 (27.0)	18.9-47.4	202/1032
Psychosis NOS, n (%)	9 (3.2)	7.3-14%	40 (3.5)	15.1-25	84/514
Schizophreniform disorder, n (%)	55 (19.2)	12-32.5%	344 (29.9)	19-41.9	202/1032
Schizoaffective disorder n (%)	25 (8.8)	5.1-28%	102 (8.8)	6.6-14	202/1032
Brief psychosis, n (%)	5 (1.8)	12%	22 (1.9)	2.2-8	43/514
Delusional disorder, n (%)	2 (0.6)	5%	17 (1.4)	2.2-5	43/514
Other non-affective psychosis, n (%)	85 (29.7)	13.7-65.8	143 (12.7)	16.9-54.8	200/637
Affective psychosis, Total, n (%)	22 (7.8)		152 (13.2)		243/826

	Early onset psychosis patient (5 samples, n=353)		**Adult onset psychosis patients (5 samples, n=1220)**		**n, Patients: youth/adults**
Bipolar disorder, n (%)	11 (3.9)	9.4%	111 (9.6)	21.4%	118/518
Other affective psychosis, n (%)	11 (3.9)	6.1-14%	41 (3.6)	9.2-16%	168/308
Substance induced psychosis, n (%)	8 (2.8)	9.8%	19 (1.4)	16%	82/119
Co-morbid substance abuse (%)	47.8	32.1-67.8%	61.7	29.1-76.8	243/826
Mean GAF baseline	28.9	21.6-32.7	29.6	19.7-31.8	243/826
Mean GAF follow-up	59.9	59.8-64.2	58.8	51.3-62.6	192/997

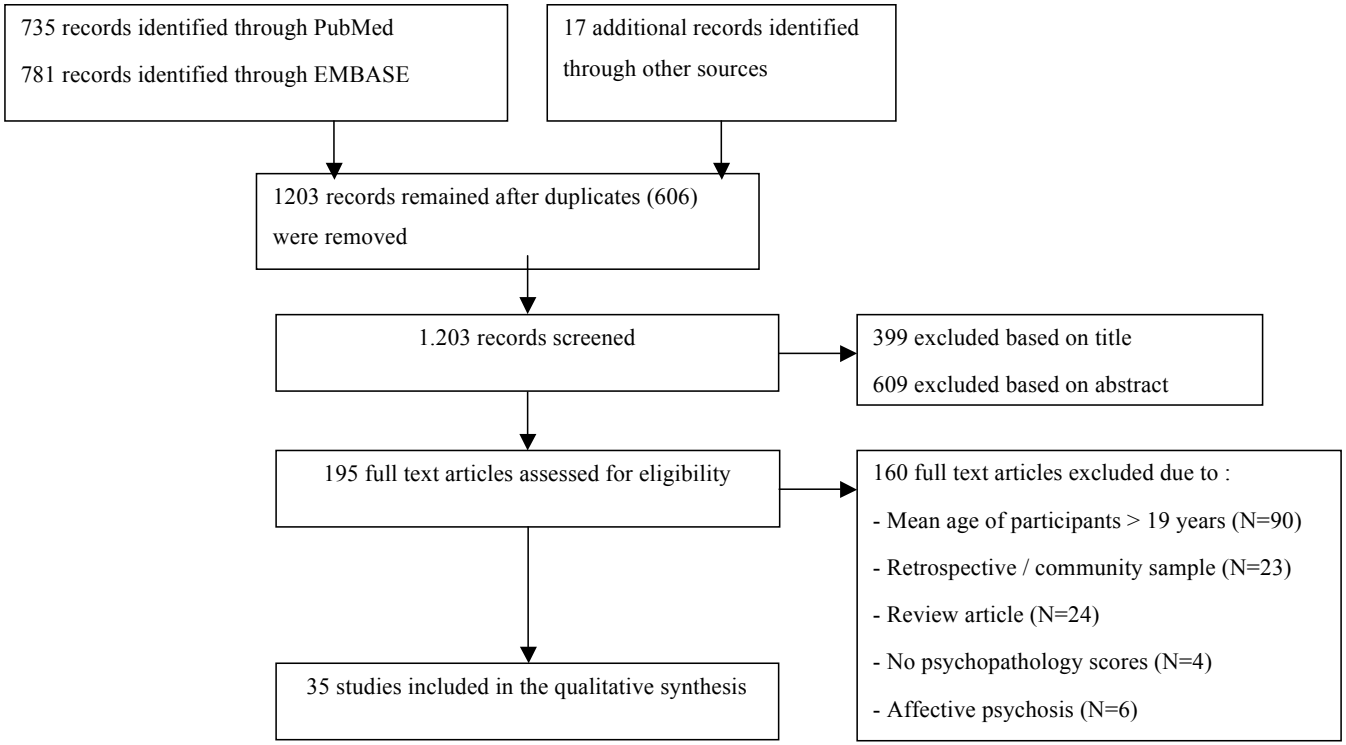
Table 8. Baseline Predictors of Outcome at 1-4 years of Follow-up in Youth with Early-onset Schizophrenia

Outcome at 1-4 Years	Baseline Predictor	Directionality	Correlation Significant	Correlation Not Significant
Illness severity (CGI-S >5)	Positive symptoms	Positive correlation	Nicolson '01	
	Negative symptoms	Positive correlation	Nicolson '01	
	Premorbid adjustment	Inverse correlation	Nicolson '01	
Negative symptoms	Premorbid adjustment	Inverse correlation	Meng '06; Castro-Fornieles '07	
Remission	Negative symptoms	Inverse correlation	Hassan '11	
	Positive symptoms	-		Hassan '11
	Premorbid adjustment	Positive correlation	Hassan '11	
Global Functioning (GAF, CGAS)	Positive symptoms	Inverse correlation	Castro-Fornieles '07	McClellan '99b; Vyas '07; Fraguas '08
	Negative symptoms	Inverse correlation	McClellan '99b; Fraguas '08; Hassan '11	Vyas '07; Castro-Fornieles '07
	Premorbid adjustment	Positive correlation	McClellan '99b; Vyas '07	
Quality of Life *	Positive symptoms	Inverse correlation	Pencer '05	
	Premorbid adjustment	Positive correlation	Pencer '05	
Social Functioning (SCS, SASS)	Negative symptoms	Inverse correlation	Meng '06; Vyas '07; Hassan '11	
	Positive symptoms	-		Meng '06; Vyas '07; Hassan '11
	Premorbid adjustment	Positive correlation	Meng '06; Vyas '07; Hassan '11	

* Quality of life at follow up also inversely associated with positive and negative symptoms at follow-up (Pencer ’05)

^ Higher scores reflect better functioning

Figure 1


735 records identified through PubMed
781 records identified through EMBASE
17 additional records identified through other sources
1203 records remained after duplicates (606) were removed
1.203 records screened
399 excluded based on title
609 excluded based on abstract
195 full text articles assessed for eligibility
160 full text articles excluded due to :
- Mean age of participants > 19 years (N=90)
- Retrospective / community sample (N=23)
- Review article (N=24)
- No psychopathology scores (N=4)
- Affective psychosis (N=6)
35 studies included in the qualitative synthesis

PAPER II

Early nonresponse determined by the clinical global impressions scale predicts poorer outcomes in youth with schizophrenia spectrum disorders naturao´listically treated with second-generation antipsychotics

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Early Nonresponse Determined by the Clinical Global Impressions Scale Predicts Poorer Outcomes in Youth with Schizophrenia Spectrum Disorders Naturalistically Treated with Second-Generation Antipsychotics

Marie Stentebjerg-Olesen, MD,[1] Pia Jeppesen, MD,[1] Anne K. Pagsberg, MD,[2] Anders Fink-Jensen, MD,[3,4] Sandeep Kapoor, MD,[5] Raja Chekuri, MD,[5] Maren Carbon, MD,[5] Aseel Al-Jadiri, MD,[5] Taishiro Kishimoto, MD,[5,6,7] John M. Kane, MD,[5,6,7,8] and Christoph U. Correll, MD[5,6,7,8]

Abstract

Objective: The use of early response/nonresponse (ER/ENR) to antipsychotics as a predictor for ultimate response/nonresponse (UR/UNR) may help decrease inefficacious treatment continuation. However, data have been limited to adults, and ER/ENR has only been determined using time-consuming psychopathology rating scales. In the current study, we assessed if early improvement on the Clinical Global Impressions-Improvement (CGI-I) scale predicted UR/UNR in psychiatrically ill youth started on antipsychotic treatment.

Methods: Seventy-nine youth aged 6–19 years, with schizophrenia spectrum disorders, treated naturalistically with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone and evaluated monthly, were divided into ER/ENR groups at week 4, using at least ''minimally improved'' on the CGI-I scale. Prediction using week 4 ER/ENR status for UR (CGI-I = at least ''much improved''), effectiveness and adverse effect outcomes at 8–12 weeks were assessed.

Results: At 4 weeks, 45.6% of subjects were ER and 54.4% were ENR without differences regarding baseline demographic, illness, and treatment variables, except for higher age ($p = 0.034$) and maximum risperidone dose ($p = 0.0043$) in ENR. ER/ENR status at 4 weeks predicted UR/UNR at week 12 significantly ($p < 0.0001$): Sensitivity = 68.9%, specificity = 85.3%, positive predictive value = 86.1%, negative predictive value = 67.4%. At weeks 4, 8, and 12, ER patients improved significantly more on the CGI-I, CGI-Severity, and Children's Global Assessment of Functioning scales, and more ER patients reached UR compared with ENR patients (83.3% vs. 34.9%, all $p < 0.0001$). ENR patients had more extrapyramidal side effects (EPS) at weeks 4, 8, and 12 ($p = 0.0019$–0.0079). UR was independently associated with ER (odds ratio [OR] = 18.09; 95% confidence interval [CI] = 4.71–91.68, $p < 0.0001$) and psychosis not otherwise specified (NOS) (OR = 4.82 [CI: 1.31–21.41], $p = 0.017$) ($r^2 = 0.273$, $p < 0.0001$).

Conclusions: Older age and EPS were associated with ENR; ENR and schizophrenia were associated with UNR in naturalistically treated youth with schizophrenia spectrum disorders. Early CGI-I-based treatment decisions require further consideration and study.

Introduction

The time course of response to antipsychotic (AP) medications in schizophrenia spectrum disorders has attracted considerable interest (Agid et al. 2003; Correll et al. 2003; Leucht et al. 2007; Kinon et al. 2008; Leucht et al. 2008; Kinon et al. 2010). This is in part because no reliable response predictors/biomarkers exist that can guide clinicians as to when to give up on a medication trial and initiate another one (Kane et al. 2003; Kane and Correll 2010; Correll et al. 2011a). In this context, a clinical marker of AP

[1]Mental Health Centre for Child and Adolescent Psychiatry, Glostrup, Denmark.
[2]Mental Health Centre for Child and Adolescent Psychiatry, Bispebjerg, Denmark.
[3]Mental Health Centre, Copenhagen, Copenhagen, Denmark
[4]Laboratory of Neuropsychiatry, Department of Neuroscience and Pharmacology, University of Copenhagen, Copenhagen, Denmark.
[5]The Zucker Hillside Hospital, Psychiatry Research, North Shore-Long Island Jewish Health System, Glen Oaks, New York.
[6]Hofstra North Shore-LIJ School of Medicine, Hempstead, New York.
[7]The Feinstein Institute for Medical Research, Manhasset, New York.
[8]Albert Einstein College of Medicine, Bronx, New York.

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response/nonresponse has gained significant traction. The focus has been on presence/absence of early improvement in the first few weeks after initiation of the AP treatment.

The hypothesis of early-onset action of APs proposes no notable delay in onset of action, and a gradual improvement toward a plateau (Agid et al. 2003). The early-onset hypothesis of AP action is opposed to the previously widely held delayed-onset of action hypothesis, according to which there is a delay of 2–3 weeks from the initiation of AP treatment to the onset of specific therapeutic effects.

Previously, it has been suggested that the early effects of APs are the result of changes in nonspecific symptoms, such as relief from anxiety and agitation, rather than a change in core psychotic symptoms. However, studies (Agid et al. 2003, Kapur et al. 2005) have shown that antipsychotic treatment leads to early and robust improvement in psychotic symptoms that is not just secondary to nonspecific changes, as the improvement is seen on psychosis-specific items on the Positive and Negative Syndrome Scale (PANSS, Kay et al. 1988) and Brief Psychiatric Rating Scale (BPRS, Overall 1974). A pooled analysis of double-blind studies including 7450 patients has shown greater improvement in the first 2 treatment weeks than in the subsequent 2 weeks, measured as reductions in total scores on the BPRS and PANSS (Agid et al. 2003). These findings have been replicated and extended to 1 year of AP treatment during which also the greatest degree of symptomatic improvement occurred in the first 2–4 weeks (Leucht et al. 2005). In one study (Kapur et al. 2005), a significant AP effect was shown to occur as early as within 24 hours of medication initiation.

More importantly, early-onset AP benefits have shown to be a stable predictor of clinical response in adults with schizophrenia (Agid et al. 2003; Kinon et al. 2010). Other studies have identified early AP nonresponse regarding total symptom scores as a robust predictor of subsequent nonresponse (Correll et al. 2003; Kinon et al. 2008; Leucht et al 2008), and early nonresponse (ENR) has been associated with less reduction in positive and negative symptoms (Lambert et al. 2007). In most studies, early response/nonresponse (ER/ENR) has been defined as $\geq 20/<20\%$ reduction on the PANSS or BPRS. In addition to predicting greater symptom reduction at study endpoint and overall treatment response as measured by at least 20% or 40% reduction in the PANSS or BPRS total score, there have also been significant differences between early responders and early nonresponders in other domains not directly related to PANSS or BPRS scores. These have included more favorable outcomes in early responders regarding higher rates of remission (Schennach-Wolff et al. 2010), longer time to all-cause treatment discontinuation (Liu-Seifert et al. 2005), lower overall and non-medication related treatment cost (Ascher-Svanum et al. 2008a), and higher levels of social and physical functioning as measured by the SF 36® (Ascher-Svanum et al. 2008a).

Although several studies have investigated the early onset of action hypothesis, there is no clear consensus on the definition and the predictive value of ER of AP drugs (Schennach-Wolff et al. 2010). This is because studies have included different patient populations regarding duration of illness and used different response and remission criteria (Correll et al. 2011b). Moreover, ER patterns, which are measured relative to baseline, also depend upon baseline illness severity (Lambert et al. 2009).

These methodological differences may have affected the results. For example, the time to predictive response may need to be much longer than 2 weeks in first-episode patients. As studies in first-episode schizophrenia spectrum disorder patients have found predictive improvement after as long as 6 weeks (Derks et al. 2010), 8 weeks (Emsley et al. 2006), or 10 weeks (Gallego et al. 2011), there may be a mixture of patient groups with early and with more delayed response patterns early on in the illness course.

Moreover, the demonstration of improved outcomes in early responders versus early nonresponders is generally based on group means. To provide a more fine-grained appraisal, recent studies have focused on trajectories of response. For example, Levine et al. (2010) identified five treatment response trajectories characterized by varying levels of symptomatic improvement. In this study, group members with better treatment response trajectories had the shortest duration of illness and the lowest dropout rates.

Moreover, to date, it has been unclear how these findings can be translated into clinical practice, as clinicians generally do not have the time to conduct a full PANSS or BPRS rating as part of their care. Conversely, the Clinical Global Impressions-Improvement scale (CGI-I, Guy 1976) is a simple, seven point Likert scale that can easily be utilized in busy clinical settings (Berk et al. 2008). It has the advantages of being simple and not time-consuming, and having clinical face validity. In addition, the CGI-I scores have been correlated to PANSS and BPRS total score reductions in equipercentile ranking studies by Leucht and colleagues (Leucht et al. 2006). In these analyses, a 20% reduction in the PANSS or BPRS scale was equivalent to a rating of ''minimally improved'' on the CGI-I, whereas a rating of ''much improved'' on the CGI-I corresponded to a reduction of 40–50% in the PANSS or BPRS total score.

However, to date, no study has attempted to assess if one can predict ultimate response (UR) reliably by presence/absence of ER defined by a rating of at least minimal improvement on the CGI-I. Post-hoc analyses in studies in which CGI as well as PANSS or BPRS assessments were obtained cannot be used to test this hypothesis, as ratings on the more detailed psychopathology scale very likely affect CGI ratings. Furthermore, to our knowledge, the hypothesis of early onset of AP effects has not been tested in children and adolescents with schizophrenia spectrum disorders, and most analyses included patients from randomized controlled studies, which may reduce the generalizability of the findings.

To fill this gap in the literature, we analyzed data from an ongoing study of children and adolescents who are treated naturalistically with AP medications based on clinical need, aiming to assess if 1) presence/absence of at least minimal improvement on the CGI-I at week 4 is a significant predictor of response/nonresponse at week 12, 2) the ER paradigm extends to patients with psychotic disorder not otherwise specified (NOS) in addition to schizophrenia, and 3) ER predicted by CGI-I at week 4 is associated with better outcomes in other efficacy and tolerability domains.

Methods

Study setting and design

Data were collected as part of the Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) study (Correll et al. 2009), an ongoing inception cohort study of AP use in youth. From December 2001 to September 2007, patients were recruited from pediatric inpatient and outpatient services of The Zucker Hillside Hospital, Queens, New York. Legal guardians/participants ages 18–19 years of age signed informed consent, minors ages 9–17 years signed informed assent, and minors <9 years old were exempt from signing assent for this North Shore-Long Island Jewish Health System Institutional Review Board-approved study.

Subjects

Inclusion criteria for the SATIETY study (Correll et al. 2009) were: Age 4–19 years; psychosis, mood, or aggressive spectrum disorder prompting clinician's choice of AP initiation; and consent/baseline assessments obtained within ≤7 days of new AP initiation. Exclusion criteria were: Treatment with >1 AP; active/past eating disorder; biochemical evidence of thyroid dysfunction; acute medical disorders; pregnancy/breastfeeding; wards of the state (as research consent by a public agency representative within 1 week was unlikely); and anticipated leaving of the catchment area within <4 weeks.

Data for this report were restricted to youth with 1) American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV; American Psychiatric Association 1994) schizophrenia spectrum disorders (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, and psychotic disorder not otherwise specified [PsyNOS]); 2) at least a 4 week and either 8 or 12 week CGI-I, (Guy 1976) assessment (in order to determine early as well as UR/UNR); 3) non-clozapine AP treatment; and 4) confirmed AP adherence (i.e., taking ≥70% of the prescribed medication based on interview, not interrupting AP treatment against medical advice for >5 half-lives, and measurable AP blood levels).

Treatment

Patients received clinician's choice of AP treatment. Informed consent/assent was obtained after the AP choice was made by the treating clinician. Dosing, co-medications and treatment changes were based on clinical necessity. Although this study focused on second-generation APs (SGAs), patients starting any AP were screened.

Outcomes

Primary outcome for the current study were the sensitivity and specificity of ER/ENR defined as a CGI-I (Guy 1976) score of at least ''minimally improved'' (corresponding to at least a 20% reduction in the PANSS or BPRS total score, [Leucht et al. 2006]) for predicting UR/UNR, defined as a CGI-I score of at least ''much improved'' (corresponding to at least a 40–50% reduction in the PANSS or BPRS total score [Leucht et al. 2006]) at last-observation-carried-forward (LOCF) study endpoint (i.e., week 8 or 12). Secondary outcomes included the predictive value of ER/ENR for UR/UNR in patient subgroups (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder vs. PsyNOS; AP-naïve vs. non-naïve patients), as well as changes in illness severity (CGI-I, CGI-Severity [CGI-S; Guy 1976]), functional status Children's Global Assessment Scale (CGAS; Shaffer et al. 1983), treatment response (i.e., CGI-I: much or very much improved), all-cause and specific-cause discontinuation, duration of inpatient stay (for inpatients only), as well as adverse effects (i.e., incidence of akathisia, Parkinsonian side effects, absolute and relative body weight and sex- and age-adjusted body mass index change, as well as the incidence of weight gain ≥7%).

Assessments

At baseline, psychiatric diagnoses, based on DSM-IV criteria, race/ethnicity, socioeconomic status, and past treatment history were assessed by chart review, discussion with treatment providers, and clinical interview of the patient/caregiver. Structured research interviews were not conducted. Socioeconomic status was categorized according to Hollingshead (1975), ranging from 1 (highest) to 5 (lowest). Postpubertal status (Tanner stage 3–5) was determined at baseline through inspection and interview of the patient and/or caregiver.

Psychopathology and adverse effect ratings in this open, naturalistic study were mostly conducted by author C.U.C. Three additional raters were trained during the course of the study by C.U.C. with regular recalibration, but without formal inter-rater reliability testing. At baseline and monthly, CGI-S was used to rate illness severity on a scale of 1 (normal, not at all ill) to 7 (extremely ill). At monthly postbaseline assessments, the CGI-I was used to rate illness improvement on a scale from 1 (very much improved) to 7 (very much worse). At baseline and monthly, the CGAS was used to assess symptomatic as well as psychosocial functioning. CGAS is a numeric scale that ranges from 0 to 100, the highest scores being the highest functioning. Quality of Life was measured with the Sheehan Disability Scale (Sheehan 1983), but the scale was introduced midstream into the study. Because of limited data in the current study sample, data were not analyzed.

For the purposes of this study, we selected *a priori* extrapyramidal side effects (EPS), akathisia, and weight change as potential correlates of early or ultimate response status, as these are easily assessed in clinical care, are related to the degree of dopaminergic blockade (EPS, akathisia) and have relevance for subjective well-being, compliance and physical health. At baseline and monthly, subjects were assessed after ≥8 hours of overnight fasting for height, body weight, and fasting laboratory values (metabolic data were not analyzed for this study). Height was measured three times, using the stadiometer Seca 214. Body weight was measured using the Tanita Body Composition Analyzer TBF-310. As described before (Correll et al. 2009), patients were weighed clothed, with emptied pockets and without shoes or socks, using the following subtraction schedule: Persons >5 feet wearing long trousers and long-sleeve shirt/sweatshirt: −3 lbs; if dressed with short pants or short-sleeve/light shirt: −2.5 lbs; if dressed with short pants and short-sleeve/light shirt: −2 lbs; if just wearing underwear: −1.5 lbs. For persons measuring <5, but >4 feet, an additional 0.5 lbs were subtracted from the formula. For persons <4 feet, an additional 1 lb was subtracted. Sex- and age-adjusted BMI *z*-scores were calculated using a web-based calculator (http://www.kidsnutrition.org/bodycomp/bmiz2.html).

Presence of EPS was assessed with the Simpson–Angus Scale (SAS; Simpson and Angus 1970) and defined as at least one item being rated mild or higher (excluding tremor and glabellar tap, as these can be affected by other non-EPS related conditions [e.g., autism, mental retardation] or medications [e.g., lithium]). Akathisia was defined as a score of at least mild (score of 2) on the global clinical assessment (range 0–5) on Barnes Akathisia Scale (BARS; Barnes 1989).

AP treatment adherence was assessed through patient and caregiver interview as well as monthly AP blood levels. AP plasma levels were measured with liquid chromatography at Cooper Laboratory (Nathan Kline Institute, Orangeburg, NY).

Statistical analyses

Patients with two or more postbaseline assessments (4 weeks to establish ER status and at least one additional assessment at 8 and/or 12 weeks to assess outcome) comprised the modified intent-to-treat sample. Consistent with prior studies in this area, LOCF analyses were utilized throughout. As mentioned, ER was defined as a rating of at least ''minimally improved'' (i.e., ≤3) on the

CGI-I at 4 weeks. Subsequently, ENR was defined as a rating of ''no change'' or worse (i.e., ≥ 4) on the CGI-I at 4 weeks. UR was defined as a rating of ''much improved'' or ''very much improved'' (i.e., 1 or 2) on the CGI-I at 8–12 weeks, and UNR was defined as a rating of ''minimally improved'' or worse (i.e., CGI-I ≥ 3) at 8–12 weeks.

For the primary outcome, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for patients with ER/ENR regarding UR, using χ^2 tests for the overall 2×2 outcome table. Sensitivity was defined as the proportion of ultimate responders at 12 weeks who were identified as early responders at 4 weeks (''true positive''). Specificity was defined as the proportion of early nonresponders at 12 weeks who were identified as early nonresponders at 4 weeks (''true negative''). The PPV was defined as the proportion of early responders at week 4 who were ultimate responders at week 12, and the NPV was defined as the proportion of nonresponders at week 4 who were ultimate nonresponders at week 12.

As up until now, the ER paradigm has been assessed only in patients with schizophrenia, we performed exploratory subgroup analyses for patients with a diagnosis of schizophrenia/schizoaffective/schizophreniform disorder or of psychosis NOS/brief psychotic disorder, and in AP-naïve patients or AP non-naïve patients.

Further, we compared baseline values across ER and ENR groups, using χ^2 or Fisher's exact tests for categorical variables and *t* test for continuous variables. As EPS and AP doses were larger in the ENR groups, we also conducted an exploratory logistic regression analysis, investigating the effect of EPS on UR status, covarying the analysis for mean AP chlorpromazine equivalent doses. Finally, we conducted a backward elimination logistic regression analysis of UR, entering ENR status, EPS during the 12 week treatment period, and all baseline variables that were statistically significantly different between ER and ENR patients (i.e., age), as well as diagnostic subgroup (i.e., schizophrenia/schizoaffective/schizophreniform disorder or PsyNOS/brief psychotic disorder) and AP-naïve status in the initial model. For categorical variables remaining significant in this model predicting UR, we further calculated the number-needed-to-treat by dividing 1 by the difference between the two UR rates.

All data were analyzed with JMP 5.0.1, 1989–2003 (SAS Institute, Inc, Cary, NC). All tests were two sided, and α was set at < 0.05.

Results

Patient population

Of 175 screened patients with a schizophrenia spectrum diagnosis, 79 patients were not consented into the study because they were either ineligible ($n = 46$) or refused consent ($n = 33$) (Fig. 1). Therefore, 96 (54.9%) patients with schizophrenia spectrum disorders were consented into the SATIETY study. Of these, 79 (82.3%) were included in the final analyses and 17 were excluded because of partial or full nonadherence based on the interview, or unmeasurable AP blood levels after baseline ($n = 12$), dropping out after week 4 ($n = 4$), or treatment with clozapine ($n = 1$) (Fig. 1). The 96 ($n = 79 + n = 17$) refusing/ineligible/excluded patients were not significantly different from the 79 included patients except for the following differences between included and excluded patients: 1) More schizophrenia and schizophreniform disorder diagnoses (32.9% vs. 8.6% $p = 0.00095$), less pervasive developmental disorder (PDD) NOS among the excluded patients (84.0% vs. 63.3%, $p = 0.00095$), and more AP-naïve patients in the included group (77.2% vs. 58.0%, $p = 0.034$).

Baseline characteristics

Patients were on average 15.2 ± 2.8 years old (range: 6.6–19.8), predominantly male (58.2%), postpubertal (86.1%), and had a wide ethnic distribution (Table 1). Most of the patients had a primary diagnosis of PsyNOS (63.3%) or schizophrenia (29.1%). The most common comorbid diagnoses were attention-deficit/hyperactivity disorder (ADHD) (12.7%), lifetime substance use disorder (12.7%), and anxiety disorders (11.4%). Altogether, 33 patients (60%) had a psychiatric family history and 14 (25.4%) had a first- or second-degree relative with schizophrenia.

There were no significant differences between ENR and ER patients in gender, race, socioeconomic status, body weight, number of past admissions, or inpatient status, except for older age in ENR patients (15.8 ± 2.4 vs. 14.5 ± 3.3 years, $p = 0.034$). Similarly, patients in both groups had equivalent levels of psychopathology and global functioning at baseline, with an average CGI-S score of 5.6 ± 0.8 (i.e., between ''markedly ill'' and ''severely ill'') and a mean CGAS of 34.0 ± 8.8 (i.e., ''major impairment in several areas and unable to function in one area'') (Table 1).

Treatment characteristics

Most patients (77.2%) were AP-naïve (i.e., ≤ 7 days of lifetime treatment) at baseline (Table 2). The most common AP prescribed was risperidone (45.6%), followed by olanzapine (20.3%), aripiprazole (17.7%), quetiapine (11.4%), and ziprasidone (5.1%).

There were no differences in treatment characteristics between the ER and ENR groups, except for the maximum daily dose of risperidone (2.2 ± 1.6 vs. 4.0 ± 1.9 mg, $p = 0.0043$), risperidone dose at 4 and 8 weeks, and risperidone level at 8 weeks (data not shown). However, across all APs together, there were no significant differences in maximum daily chlorpromazine equivalent doses or in mean chlorpromazine equivalent doses at week 4, 8, and 12 (Table 2).

A minority of 27 patients (34.6%) received no co-medications during the 12 week study. The co-medications primarily used were antidepressants (25.6%), anxiolytics/sedatives (18%), and anticholinergics (16.7%). There was no difference in the use of co-medications between the ER and ENR groups.

Response trajectory

At week 4, 36 patients (45.6 %) were ER and 43 (54.4 %) were ENR, using a CGI-I of ≤ 3 threshold. At week 12, 45 patients (57.0%) were UR and 34 (43%) were UNR, using a threshold of CGI-I ≤ 2.

Predictive value of ER/ENR

The predictive value analysis (Table 3) of early ER/ENR predicting UR/UNR showed a specificity of 85.3%, an NPV of 67.4%, a sensitivity of 68.9%, and a PPV of 86.1% (χ^2 $p < 0.0001$).

The exploratory subgroup analyses in patients with PsyNOS/brief psychosis or schizophrenia/schizoaffective disease showed a higher sensitivity and, especially, NPV for patients with schizophrenia than for PsyNOS (sensitivity: 83.3% vs. 63.6%, NPV: 86.7% vs. 57.1%). By contrast, specificity and, especially, PPV were higher in PsyNOS patients (specificity: 88.9% vs. 81.3%, PPV: 91.3% vs 76.9%). Similarly, in the AP-naïve subgroup, specificity and PPV were higher than in the patients with prior AP exposure history (specificity: 91.7% vs. 70.0%, PPV: 92.6% vs. 66.7%) whereas sensitivity and NPV were only slightly higher in AP-exposed patients (sensitivity: 75.0% vs. 67.6%, NPV: 77.8% vs. 64.7%).

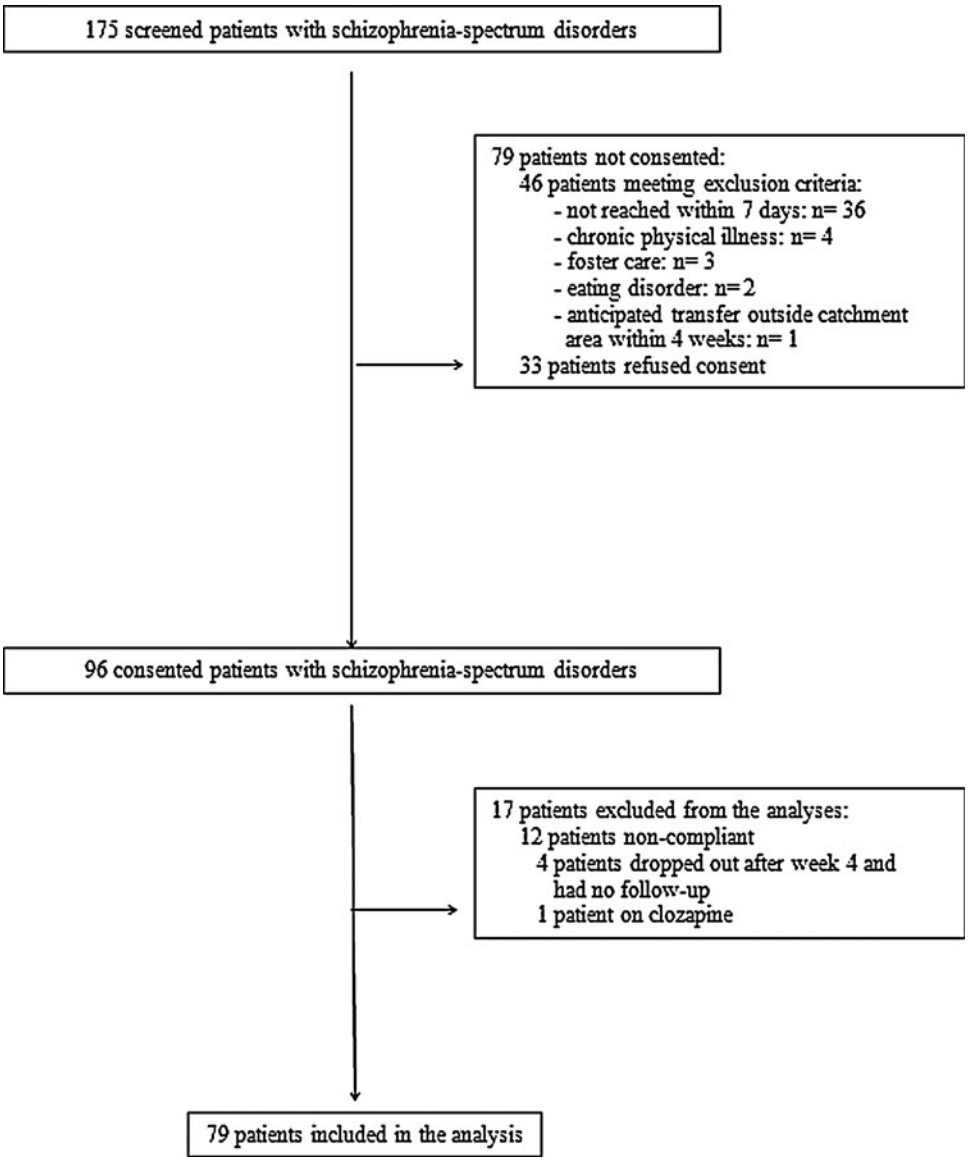

FIG. 1. Patient flow.

Efficacy, effectiveness and tolerability outcomes

Compared with ENR patients, ER patients had significantly better scores at every visit in CGI-I, CGI-S, and CGAS (all $p < 0.0001$) (Table 4). At week 12, significantly more ER patients than ENR patients reached UR status (83.3% vs. 34.9%, $p < 0.0001$, number-needed-to-treat: 3).

The total rate of all cause discontinuation was 24.4%, and there was a trend for ENR patients to discontinue treatment more often than ER patients (33.3% vs.13.9%, $p = 0.064$). This was primarily the result of more ENR patients discontinuing because of inefficacy ($p = 0.061$) (Table 4).

Side effects

Altogether, 30.8% of patients had at least mild EPS at least at one postbaseline assessment. A significantly higher proportion of ENR patients had EPS at weeks 4, 8, and 12 compared with ER patients ($p = 0.0019$–0.0079) (Table 4). Occurrence of any EPS during the 12 week study was significantly associated with ENR status, both in univariate analyses (46.2% vs. 12.2%, $p = 0.0018$), as well as after controlling for AP-naive status and chlorpromazine equivalent AP doses ($p = 0.0029$).

Only a few patients (7.8%) developed akathisia during the study, and there was no significant group difference in the incidence of akathisia between the ER and ENR groups. At week 12, patients had gained an average of 5.7 ± 4.3 kg and 51 (64.5%) had gained at least 7% of their baseline body weight, but ER and ENR patients also did not differ regarding these outcomes.

Logistic regression model of ultimate response

Entering age, diagnostic subgroup, AP-naïve status at baseline, and ER status as well as EPS during the study period into the model, the following two variables emerged as independent predictors of UR ($r^2 = 0.273$, $p < 0.0001$): ER status at week 4 (odds ratio [OR]: 18.09, 95% confidence interval [CI]: 4.71–91.68, $p < 0.0001$), and PsyNOS/brief psychotic disorder (OR: 4.82, 95% CI: 1.31–21.41, $p = 0.017$).

Table 1. Baseline Demographic and Illness Characteristics

Demographic and illness characteristics	*Total* (n = *79*)	*Early responder* (n = *36*)	*Early nonresponder* (n = *43*)	p *value*
Age, years, mean ± SD	15.2 ± 2.8	14.5 ± 3.3	15.8 ± 2.4	**0.034**
Postpubertal status, *n* (%)	68 (86.1)	28 (77.8)	40 (93.0)	0.10
Sex male, *n* (%)	46 (58.2)	22 (61.1)	24 (55.8)	0.64
Race, *n* (%)				0.91
Caucasian	29 (36.7)	13 (36.1)	16 (37.2)	
Black/African-American	27 (34.2)	14 (38.9)	13 (30.2)	
Hispanic	11 (13.9)	5 (13.9)	6 (14.0)	
Asian	6 (7.6)	2 (5.6)	4 (9.3)	
Other	6 (7.6)	2 (5.6)	4 (9.3)	
Inpatients, *n* (%)	62 (78.5)	30 (83.3)	32 (74.4)	0.34
Number of past admissions, mean ± SD	0.2 ± 0.6	0.1 ± 0.5	0.3 ± 0.6	0.27
Socioeconomic status, mean ± SD	2.6 ± 0.9	2.7 ± 0.9	2.6 ± 1.0	0.82
Weight, kg, mean ± SD	57.6 ± 16.2	57.3 ± 18.3	57.8 ± 14.2	0.89
BMI %-tile, mean ± SD	54.5 ± 30.9	58.3 ± 32.4	52.3 ± 29.6	0.32
Weight status, *n* (%)				0.31
Underweight	6 (7.6)	3 (8.3)	3 (7.0)	
Normal weight	56 (70.9)	22 (61.1)	34 (79.1)	
Overweight	6 (7.6)	4 (11.1)	2 (4.7)	
Obese	11 (13.9)	7 (19.4)	4 (9.3)	
Primary diagnosis, *n* (%)				0.92
Psychotic disorder not otherwise specified	50 (63.3)	22 (61.1)	28 (65.1)	
Schizophrenia	23 (29.1)	11(30.6)	12 (27.9)	
Schizophreniform disorder	3 (3.8)	1 (2.8)	2 (4.7)	
Schizoaffective disorder	2 (2.5)	1 (2.8)	1 (2.3)	
Brief psychotic disorder	1 (1.3)	1 (2.8)	0 (0)	
CGI-S, mean ± SD	5.6 ± 0.8	5.7 ± 0.9	5.6 ± 0.8	0.66
CGAS, mean ± SD	34.0 ± 8.8	33.6 ± 8.1	34.2 ± 9.3	0.78
Psychiatric family history, *n* (%)				
Any psychiatric disorder	33 (60.0)	11 (50.0)	22 (66.7)	0.22
Schizophrenia family history				
First degree relative	2 (3.6)	2 (9.1)	0 (0)	0.16
Second degree relative	12 (21.8)	4 (18.2)	8 (24.2)	0.74
Comorbidity, *n* (%)				
Attention-deficit/hyperactivity disorder	10 (12.7)	7 (19.4)	3 (7.0)	0.17
Lifetime substance use disorder	10 (12.7)	5 (13.9)	5 (11.6)	1.00
Anxiety disorder	9 (11.4)	5 (13.9)	4 (9.3)	0.73
Disruptive behavior disorders[a]	6 (7.6)	4 (11.1)	2 (4.7)	0.40
Obsessive compulsive disorder	5 (6.3)	2 (5.6)	3 (7.0)	1.00
Pervasive developmental disorder	3 (3.8)	1 (2.8)	2 (4.7)	1.00
Depressive spectrum disorders[b]	3 (3.8)	2 (5.6)	1 (2.3)	0.59
Mental retardation	4 (5.1)	1 (2.8)	3 (7.0)	0.62

[a]Disruptive behavior disorders = oppositional defiant disorder, conduct disorder, intermittent explosive disorder, impulse control disorder not otherwise specified.

[b]Depressive spectrum disorders = major depressive disorder, depressive disorder not otherwise specified, adjustment disorder with depressed mood.

CGAS, Children's Global Assessment of Functioning Scale; CGI-S, Clinical Global Impressions-Severity.

Bolded *p*-values indicate $p < 0.05$.

Discussion

In this first study that utilized the clinically scalable CGI-I assessment as the sole tool to categorize patients into ER and ENR groups, ER or ENR at week 4 accurately predicted subsequent response or nonresponse at week 12 in youth with schizophrenia spectrum disorders who were primarily AP naïve and treated naturalistically with SGAs. Moreover, ER patients had significantly greater improvements in CGI-S and CGAS scores than ENR patients. Furthermore, ENR status was predicted by higher age and EPS ratings, whereas UNR status was predicted by ENR and a diagnosis of schizophrenia.

Studies in adults with chronic schizophrenia have repeatedly shown that ER or ENR to APs at week 1 or 2, generally defined as at least a 20% reduction in PANSS or BPRS total score, is a robust predictor of later response or nonresponse (Correll et al. 2003; Leucht et al. 2007; Ascher-Svanum et al. 2008a; Kinon et al. 2008; Leucht et al. 2008; Kinon et al. 2010; Hatta et al. 2011). Moreover, these studies have also shown that early AP treatment response is associated with significantly better outcomes, indicated by greater improvements on scales and dimensions not directly related to PANSS or BPRS scores that were used to group patients into ER and ENR subjects (Correll et al. 2003; Leucht et al. 2007; Ascher-Svanum et al. 2008a; Kinon et al. 2008; Leucht et al. 2008; Kinon et al. 2010; Hatta et al. 2011). However, to date, all studies that have investigated the predictive validity of early clinical response for later response included adult patients in randomized controlled or open-label trials, and used changes on the PANSS or BPRS as measures of ER/ENR and of UR.

Table 2. Treatment Characteristics

Treatment characteristics	± *Total (*n = *79)*	*Early responder (*n = *36)*	*Early nonresponder (n = 43)*	p *value*
Antipsychotic- naïve, *n* (%)	61 (77.2)	27 (75.0)	34 (79.1)	0.67
Number of antipsychotic trials (mean ± SD)	0.5 ± 0.9	0.6 ± 1.1	0.4 ± 0.7	0.44
Antipsychotic treatment				
Risperidone, *n* (%)	36 (45.6)	18 (50.0)	18 (41.9)	0.47
Starting dose (mg ± SD)	0.8 ± 0.5	0.7 ± 0.4	0.9 ± 0.6	0.16
Days until max dose (mean ± SD)	24.6 ± 23.8	20.5 ± 24.3	28.8 ± 23.4	0.32
Maximum daily dose (mg ± SD)	3.1 ± 1.7	2.2 ± 1.6	4.0 ± 1.9	**0.0043**
Olanzapine, *n* (%)	16 (20.3)	7 (19.4)	9 (20.9)	0.87
Starting dose (mg ± SD)	3.0 ± 1.1	3.6 ± 1.3	2.6 ± 1.0	0.13
Days until max dose (mean ± SD)	26.5 ± 27.8	29.0 ± 28.3	24.4 ± 27.2	0.75
Maximum daily dose (mg ± SD)	12.6 ± 7.4	14.3 ± 7.9	11.3 ± 7.0	0.43
Aripiprazole, *n* (%)	14 (17.7)	4 (11.1)	10 (23.3)	0.24
Starting dose (mg ± SD)	5.2 ± 4.5	3.1 ± 1.3	6.1 ± 5.2	0.29
Days until max dose (mean ± SD)	31.2 ± 26.9	24.0 ± 19.0	34.1 ± 29.0	0.54
Maximum daily dose (mg ± SD)	17.0 ± 9.0	14.4 ± 7.7	18.0 ± 9.4	0.51
Quetiapine, *n* (%)	9 (11.4)	5 (13.9)	4 (9.3)	0.73
Starting dose (mg ± SD)	45.8 ± 35.3	45.0 ± 32.6	46.9 ± 38.7	0.94
Days until max dose (mean ± SD)	22.0 ± 19.0	17.8 ± 22.9	27.3 ± 11.8	0.48
Maximum daily dose (mg ± SD)	369.4 ± 270.2	310.0 ± 214.0	443.8 ± 330.6	0.49
Ziprasidone, *n* (%)	4 (5.1)	2 (5.6)	2 (4.7)	1.00
Starting dose (mg ± SD)	25.0 ± 10.0	20.0 ± 0	30.0 ± 14.1	0.42
Days until max dose (mean ± SD)	20.8 ± 10.7	23.5 ± 13.4	18.0 ± 7.1	0.66
Maximum daily dose (mg ± SD)	120.0 ± 44.7	100.0 ± 56.6	140.0 ± 28.3	0.47
Pooled CPZ equivalent doses (mg ± SD)				
Mean pooled maximum CPZ equivalent dose	228.0 ± 184.7	198.2 ± 173.2	253.5 ± 194.0	0.19
Mean CPZ equivalent dose at week 4	182.6 ± 149.0	159.6 ± 110.1	201.4 ± 174.3	0.22
Mean CPZ equivalent dose at week 8	205.9 ± 171.3	180.5 ± 153.5	228.2 ± 185.4	0.23
Mean CPZ equivalent dose at week 12	205.9 ± 189.6	188.0 ± 182.1	220.1 ± 195.2	0.46
Co-medication				
Total number of co-medications	0.9 ± 0.9	0.9 ± 0.7	0.9 ± 1.1	0.95
None, *n* (%)	27 (34.6)	10 (27.8)	17 (40.5)	0.24
Antidepressants, *n* (%)	20 (25.6)	9 (25.0)	11 (26.2)	0.91
Mood stabilizers, *n* (%)	11 (14.1)	5 (13.9)	6 (14.3)	1.00
Stimulants, *n* (%)	3 (3.9)	2 (5.6)	1 (2.4)	0.59
Anticholinergics, *n* (%)	13 (16.7)	5 (13.9)	8 (19.1)	0.76
Anxiolytics-sedatives, *n* (%)	14 (18.0)	7 (19.4)	7 (16.7)	0.75
α-agonists, *n* (%)	3 (3.9)	2 (5.6)	1 (2.4)	0.59
Other co-medications	4 (5.1)	3 (8.3)	1 (2.4)	0.33

CPZ, chlorpromazine.
Bolded *p*-values indicate $p < 0.05$.

This study extends the prior research in several ways. Most importantly, we examined pediatric patients in a naturalistic treatment setting, and we used the CGI-I rating for the assessment of ER and UR, both features that increase the generalizability and clinical applicability of the findings. Moreover, we included a majority of patients with PsyNOS, a diagnostic group that has not been examined with the ER paradigm.

We found that a CGI-I of less than ''minimally improved'' at week 4 was a significant predictor of UNR status (defined as a CGI-I > 2) as well as of significantly less improvement on the CGI-S and CGAS at weeks 8 and 12. Specificity level for the prediction of UNR was high (85.3%), indicating a high probability that nonresponders at week 12 were correctly identified at week 4. High specificity and high NPV are needed to avoid unnecessarily changing treatment in patients who would have responded. PPV was also high (86.1%), whereas sensitivity (68.9%) and NPV (67.4%) were moderate. For patients with schizophrenia and for AP-non-naïve patients the NPV (86.7% and 77.8%, respectively) was higher than for the entire cohort of patients that included a larger proportion of patients with PsyNOS. These results indicate that a diagnosis of schizophrenia or a prior exposure to APs seem to improve the predictive value of ENR to antidopaminergic medications in this patient group. This finding is in line with analyses in adult first-episode schizophrenia samples in whom the 2 week predictive value of ENR was generally not as good as seen in chronically ill patients (Emsley et al. 2006; Gallego et al. 2011; Stauffer et al. 2011). On the other hand, we found that the PPV of ER is very high among patients with PsyNOS/brief psychosis.

For example, one study of predominantly adults (16–40 years of age) with first-episode schizophrenia (Stauffer et al. 2011) examined early response to AP treatment, defined as a 26.2% improvement on the PANSS total score at week 2, as a predictor of response at week 12 (defined as ≥ 50% reduction of the PANSS total score). These thresholds for ER and UR are comparable to the ones used in our study, according to an equipercentile ranking that linked ratings of levels of illness severity and improvement measured on the CGI-S and CGI-I to ratings on the PANSS or BPRS total score (Leucht et al. 2006). In that study, a 20% reduction in total BPRS or

Table 3. Predictive Value Analysis of Early Response at Week 4 for Ultimate Response at Weeks 8–12 (LOCF)

Sample	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	p *value of 2×2 table*
Total sample ($n=79$)	68.9%	85.3%	86.1%	67.4%	**<0.0001**
Subgroup analysis by diagnostic groups					
Schizophrenia/Schizoaffective disorder ($n=28$)	83.3%	81.3%	76.9%	86.7%	**0.0016**
Psychosis NOS/ Brief psychotic disorder ($n=51$)	63.6%	88.9%	91.3%	57.1%	**0.0004**
Subgroup analysis by treatment history					
Antipsychotic-naïve ($n=61$)	67.6%	91.7%	92.6%	64.7%	**<0.0001**
Antipsychotic-non-naïve ($n=18$)	75.0%	70.0%	66.7%	77.8%	0.15

LOCF = last-observation-carried-forward; NOS, not otherwise specified.
Bolded *p*-values indicate $p<0.05$.

PANSS score was comparable to ''minimally improved'' on the CGI-I, and a 40–50% reduction in total BPRS or PANSS score was comparable to rating of at least ''much improved'' on the CGI-I.

Two weeks was chosen as the early response assessment time point in the study by Stauffer et al. (2011), as in many other studies, on the basis of previous investigations, in which the bulk and/or significantly greater improvement in symptoms occurred during weeks 1 and 2 of treatment compared with weeks 3 and 4 (Agid et al. 2003; Leucht et al. 2005). Stauffer and colleagues found 43.1% of patients to be early responders, which is almost the same as the 45.6% early responders in our study, although early response in our study was measured at 4 and not 2 weeks. However, in the adult first-episode sample, using a ≥50% reduction on the PANSS total score for UR, only 39% of patients had UR at week 12 compared with 57% in our study in which a CGI-I of ''much or very much improved'' defined UR. However, the study by Stauffer et al. (2011) had only 21.6%/30.5% AP-naïve patients in the ER/ENR groups, respectively, compared with 75.0%/79.1% in our study. The two to three times higher proportion of AP-naïve patients might be part of the reason why in our sample more patients achieved UR status. Moreover, participants in our study were pediatric patients, compared with patients 16–40 years of age in the study by Stauffer et al (2011). This finding of more ultimate responders in our study suggests that PsyNOS and AP-naïveté-enriched samples or early-onset psychosis patients may have a more favorable response than adult first-episode schizophrenia patients, a finding also reported in two independent, large Australian samples (Schimmelmann et al. 2007; Amminger et al. 2011). Nevertheless, the sensitivity analysis of ER at 2 weeks to predict UR at 12 weeks in the adult first-episode sample yielded an NPV of 80% and specificity of 74%, which is comparable to the NPV of 86.7% and the specificity of 81.3% in our patient subgroup with schizophrenia and schizoaffective disorder, and to the NPV of 77.8% and specificity of 70% in our AP-non-naïve subgroup. Interestingly, in a subgroup analysis of patients ≤21 and >21 years of age, Stauffer et al. (2011) found no difference in the predictive characteristics of ER/ENR, supporting that the ER paradigm can be extended to younger age groups. Extension of the ER paradigm to adolescents was also recently confirmed by a post-hoc analysis of a randomized, placebo-controlled study, showing that ER at week 3 was most predictive (more so than at week 2) of UR and remission at week 6 in adolescents 13–17 years of age with non-first-episode schizophrenia who had been randomized to aripiprazole (Correll et al. 2013).

In our study, ER/ENR assessments were only available at week 4 after baseline and not before, whereas most prior studies focused on week 2 (or week 1). However, some studies of first-episode patients point to the importance of a later time point to determine ER/ENR status for this patient group. In an analysis of the European First Episode Study (EUFEST), the rate and predictors of remission within 12 months (according to Andreasen's remission criteria of a score of mild or less on eight predefined PANSS items, Andreasen et al. 2005) was assessed (Derks et al. 2010). All variables that were significantly associated with remission (PANSS, CGI) were included as predictors in the analyses. The authors found that the prediction of remission significantly improved by the inclusion of 4 and 6 week assessments instead of choosing only week 2, and that the CGI-S score at 4 weeks significantly improved the prediction of remission even when the PANSS rating was excluded. In another first-episode study, time to clinical response (defined as ≥20% improvement in PANNS total score) was determined (Emsley et al. 2006), and the investigators found that time to AP response varied widely and that 22.5% of patients did not respond until after 4 weeks. These results are in line with a 16 week study by Gallego et al. (2011) in which many patients responded between weeks 8 and 16, and in which percentage reduction in symptom severity score at week 4, but not at week 2 or week 8, was associated with UR status at week 16. Therefore, results from these studies indicate that a 4 week time point might be reasonable to determine ER status in first-episode or recent-onset patients.

In some early prediction studies, the same threshold for ER as for UR was used (Ascher-Svanum et al. 2008a). In our study, we chose a greater improvement threshold to determine UR than to determine ER. In two studies by Kinon et al. (2008, 2010) the greatest total predictive accuracy of early response (defined as ≥20% improvement on the PANSS total score) existed for UR using a threshold of ≥40% or ≥50% improvement in the PANSS total score, with lesser accuracy for UR definitions, using ≥20% or ≥30% improvement in PANSS total score, or Andreasen's remission criteria. These results suggest that a higher threshold for later response than for early response might be more appropriate, in addition to being also clinically more meaningful (Correll et al. 2011b).

One study of adults with chronic schizophrenia used the CGI-I to determine ER (Hatta et al. 2011), using the same ER criteria as we did (i.e., at least ''minimally improved'' on the CGI-I) but at week 2, in order to predict UR at week 4 (defined as ≥50% improvement of PANSS total score). Therefore, their threshold for later response was comparable to ours, but employed at an earlier time point. Hatta and colleagues (2011) found ER to risperidone in primarily AP-naïve patients to predict later nonresponse. Importantly, however, different from our study, the CGI ratings were not made

Table 4. Treatment Outcomes

Outcomes	*Total* (n = *79*)	*Early responder* (n = *36*)	*Early nonresponder* (n = *43*)	p *value*
All-cause discontinuation, *n* (%)	19 (24.4)	5 (13.9)	14 (33.3)	0.064
Discontinuation, reasons,[a] *n* (%)				
Inefficacy	8 (10.4)	1 (2.8)	7 (17.1)	0.061
Intolerability	9 (11.7)	3 (8.3)	6 (14.6)	0.49
Loss of contact	4 (5.2)	2 (5.6)	2 (4.9)	1.00
Number of inpatient days (mean ± SD)	25.6 ± 21.7	20.7 ± 19.5	30.1 ± 23.5	0.09
Response (CGI-I </= 2), *n* (%)	45 (57.0)	30 (83.3)	15 (34.9)	**< 0.0001**
CGI-I, mean ± SD				
4 weeks	2.6 ± 0.5	1.7 ± 0.5	3.4 ± 0.5	**< 0.0001**
8 weeks	2.4 ± 0.9	1.8 ± 1.0	3.0 ± 0.7	**< 0.0001**
12 weeks	2.1 ± 0.8	1.5 ± 0.7	2.7 ± 0.9	**< 0.0001**
CGI-S change, mean ± SD				
4 weeks	− 1.2 ± 0.8	− 1.9 ± 1.0	− 0.6 ± 0.7	**< 0.0001**
8 weeks	− 1.4 ± 1.0	− 2.0 ± 1.2	− 0.8 ± 0.8	**< 0.0001**
12 weeks	− 1.7 ± 1.2	− 2.4 ± 1.4	− 1.2 ± 1.1	**< 0.0001**
CGAS change, mean ± SD				
4 weeks	11.9 ± 7.3	18.1 ± 8.3	6.7 ± 6.4	**< 0.0001**
8 weeks	15.2 ± 9.4	20.6 ± 9.7	10.6 ± 9.1	**< 0.0001**
12 weeks	18.0 ± 11.0	23.5 ± 11.2	13.0 ± 10.8	**< 0.0001**
EPS, *n* (%)				
4 weeks	15 (21.4)	2 (6.1)	13 (35.1)	**0.0035**
8 weeks	14 (19.7)	2 (6.1)	12 (31.6)	**0.0079**
12 weeks	14 (19.4)	1 (3.0)	13 (33.3)	**0.0019**
Anytime at 4, 8 or 12 weeks	22 (30.6)	4 (12.2)	18 (46.2)	**0.0018**
Akathisia, *n* (%)				
4 weeks	5 (6.6)	2 (5.7)	3 (7.3)	1.00
8 weeks	5 (6.5)	1 (2.9)	4 (9.5)	0.37
12 weeks	4 (5.2)	1 (2.9)	3 (7.1)	0.62
Anytime at 4, 8 or 12 weeks	6 (7.8)	2 (5.7)	4 (9.5)	0.53
Weight change, kg, mean ± SD				
4 weeks	3.1 ± 2.6	3.0 ± 2.1	3.3 ± 3.0	0.64
8 weeks	4.8 ± 3.7	4.9 ± 3.0	4.8 ± 4.2	0.92
12 weeks	5.7 ± 4.3	5.5 ± 3.5	5.9 ± 4.9	0.65
Weight % change, mean ± SD, 12 weeks	11.0 ± 8.8	10.4 ± 7.0	11.6 ± 10.2	0.56
Weight gain ≥ 7%, *n* (%), 12 weeks	51 (64.5)	24 (66.7)	27 (62.8)	0.72
BMI change, kg/m^3, mean ± SD				
4 weeks	1.1 ± 0.9	1.1 ± 0.8	1.1 ± 1.1	0.91
8 weeks	1.7 ± 1.3	1.7 ± 1.1	1.6 ± 1.4	0.75
12 weeks	1.9 ± 1.5	1.9 ± 1.3	2.0 ± 1.7	0.73
BMI *z*-score change, mean ± SD				
4 weeks	0.4 ± 0.4	0.4 ± 0.4	0.4 ± 0.4	0.96
8 weeks	0.7 ± 1.0	0.8 ± 0.9	0.6 ± 1.0	0.23
12 weeks	0.6 ± 0.6	0.6 ± 0.5	0.6 ± 0.7	0.83

[a]Total may be >100% of all-cause discontinuation because of discontinuation for more than one reason.

BMI, body mass index; CGAS, Children's Global Assessment of Functioning Scale; CGI-I, Clinical Global Impressions- Improvement; CGI-S, Clinical Global Impressions-Severity; EPS, Extrapyramidal Side Effects.

Bolded *p*-values indicate $p < 0.05$.

independently of PANSS ratings. Therefore, raters' CGI sores were likely influenced by the much more time-consuming and detailed PANSS assessments. The finding of utility of CGI ratings is consistent with results by Leucht and Engel (2006) who found the CGI to be as sensitive as the BPRS in detecting efficacy differences among AP drugs; however, again, CGI and BPRS ratings were not made independent of each other. In this regard, our study adds to these results, suggesting that the clinically very feasible global CGI assessments, performed without co-rating of a detailed psychopathology scale, have acceptable and clinically useful predictive value to determine UR status early in the treatment course of a new AP trial.

Notably, we found that significantly more patients in the ENR group than in the ER group had EPS at week 4, 8, and 12, and that EPS at any time postbaseline point was associated with ENR, a finding that was independent of AP-naive status and chlorpromazine equivalent AP doses. Although in one study of chronically ill schizophrenia patients (Kinon et al. 2010), EPS was not related to ENR or UNR, EPS was related to UNR in an earlier study using first-generation APs (Kinon et al. 1993), and EPS was related to both ENR and UNR in a study of first-episode patients (Stauffer et al. 2011). In the latter study, both the ER and the ENR group had a significant worsening of Parkinsonian symptoms early on. In the last

6 weeks, EPS improved in responders, but not in nonresponders, and significant between-group differences were seen at weeks 10 and 12. These converging findings indicate that dopamine dysfunction, uncovered by EPS in response to AP treatment, is a marker of both ENR and UNR, which may be most detectable in early phase illness and AP-naïve patients. Similarly, in a previous first-episode study, baseline EPS was associated with poorer treatment response (Chatterjee et al. 1995), and tardive dyskinesia has also been associated with less AP efficacy and poorer treatment outcomes (Asher-Svanum et al. 2008b). By contrast, akathisia, which may be more related to the noradrenergic transmitter system (Wilbur et al. 1988), was not related to ENR or UNR in our or prior studies. Finally, neither we nor Stauffer and colleagues (2011) detected a significant relationship between body weight gain and either ER or UR status.

Limitations

The results from this study need to be interpreted within its limitations. These include the relatively low number of patients, large age range, mixture of schizophrenia and PsyNOS patients, lack of formal diagnostic interviews and inter-rater reliability testing of the CGI-I assessments, naturalistic treatment with comedications being permitted, the absence of CGI-I ratings before week 4, and absence of PANSS or BPRS ratings to compare the performance of the CGI with more detailed PANSS/BPRS ratings. On the other hand, absent PANSS/BPRS ratings avoided the problem of criterion conflation, in that the singular performance of the pragmatic CGI scale without incorporating rating scale-based information could be tested in a naturalistic treatment setting.

Conclusions

Older age and EPS were associated with ENR, and ENR and a schizophrenia diagnosis were associated with UNR at 12 weeks in naturalistically treated youth with schizophrenia spectrum disorders. The utility of CGI-I based early treatment decisions needs to be considered and studied further, in both youth and adults.

Clinical Significance

To our knowledge, this is the first study that demonstrated the validity of the early response paradigm in a naturalistically treated pediatric sample of mostly AP-naïve youth and those with PsyNOS. The study employed CGI ratings as a stand-alone efficacy measure that is easily scalable into clinical care. All of these features increase the generalizability and clinical relevance of these findings. To further extend these data, the utility of CGI ratings to determine ER and UR needs to be tested in general clinical settings. Moreover, studies using different raters who assess patients on the CGI and the PANSS or BPRS are needed, in order to compare the diagnostic accuracy of these two approaches. EPS ratings should be included, and the predictive value of the full Simpson–Angus scale versus a few screening items should be investigated in future studies also, in order to increase the feasibility of using early EPS assessments as an additional marker for UNR in schizophrenia spectrum patients.

Disclosures

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Address correspondence to:
Christoph U. Correll, MD
Division of Psychiatry Research
The Zucker Hillside Hospital
75-59 263rd Street
Glen Oaks, NY 11004

E-mail: ccorrell@lij.edu

PAPER III

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Figures: 1

Early Response or Nonresponse at Week 2 and Week 3 Predict Ultimate Response or Nonresponse in Adolescents with Schizophrenia Treated with Olanzapine: Results from a 6-Week Randomized, Placebo-controlled Trial

Marie Stentebjerg-Olesen, MD;[1], Stephen J. Ganocy, PhD;[2] Robert L. Findling, MD, MBA;[3] Kiki Chang, MD[4], Melissa P. DelBello, MD, MS;[5] John M Kane, MD[6,7,8,9]; Mauricio Tohen, MD, DrPH, MBA[10]; Pia Jeppesen[1], MD; Christoph U. Correll, MD[6,7,8,9]

Institutional Affiliations:

[1] Child and Adolescent Mental Health Center, Mental Health Services, the Capital Region of Denmark; Faculty of Health Science, University of Copenhagen, Denmark

[2]Case Western Reserve University, University Hospitals Case Medical Center, Cleveland, OH USA

[3]Johns Hopkins University and the Kennedy Krieger Institute, Baltimore, MD USA

[4]Stanford University School of Medicine, Stanford, CA USA

[5]University of Cincinnati, Cincinnati, OH USA

[6] The Zucker Hillside Hospital, Psychiatry Research, North Shore - Long Island Jewish Health System, Glen Oaks, New York, USA;

[7] Hofstra North Shore LIJ School of Medicine, Hempstead, NY, USA;

[8] Albert Einstein College of Medicine, Bronx, New York, USA;

[9] The Feinstein Institute for Medical Research, Manhasset, New York, USA.

[10] Department of Psychiatry University of New Mexico Health Science Center Albuquerque New Mexico USA

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Corresponding author:

Christoph U. Correll, MD, Department of Psychiatry, The Zucker Hillside Hospital, 75-59 263rd Street, Glen Oaks, NY 11004 (ccorrell@lij.edu)

Abstract

Background: In adults with schizophrenia, early response/non-response (ER/ENR) to antipsychotics as soon as at2 weeks is a robust predictor of ultimate response/non-response (UR/UNR). However, it is less clear whether the early antipsychotic response/non-response paradigm, including the threshold and best time point for establishing ENR, is equally applicable to adolescents with schizophrenia.

Methods: We conducted a post-hoc analysis of a 6-week trial in 107 adolescents aged 13-17 years with schizophrenia who were randomized 2:1 to olanzapine (n=72) or placebo (n= 35). ER was defined as ≥20% reduction in the Brief Psychiatric Rating Scale-Children (BPRS-C) total score at week 2 (ER2) or week 3 (ER3); UR was defined with increasing stringency as a total BPRS-C score reduction of ≥20%, ≥30%, ≥40% or ≥50%; remission was defined using cross-sectional consensus group criteria (i.e., ≤mild positive and negative symptom item scores).

Results: By week 2 and 3 olanzapine-treated youth (n=69) achieved already 73.3% and 85.5% of their overall BPRS-C score reduction at 6 weeks last-observation-carried-forward. ER and ENR patients did not differ significantly regarding baseline demographic, illness and treatment variables. ER 2 (frequency=68.1%), and ER 3 (frequency=65.2%) significantly predicted UR and remission ($p=0.0044$ to $p<0.0001$), with ER3 being more predictive. A threshold for ER of ≥20% BPRS-C reduction had best predictive validity (area under the curve=0.88-0.92). At 6 weeks, patients with ER had significantly greater improvements in BPRS-C, Clinical Global Impressions-Improvement and Severity scores, greater cross-sectional remission and less all-cause discontinuation ($p=0.047$ to $p<0.0001$). Except for more baseline extrapyramidal side effects in ER3 patients ($p=0.02$), adverse event profiles were similar in ER and ENR groups.

Conclusions: Adolescents with schizophrenia experienced the majority of symptomatic improvement early during olanzapine treatment. ER predicted UR and remission, with ER3 having best predictive power. A ≥20% improvement threshold for defining ER was confirmed as a robust outcome indicator.

Key Words: Schizophrenia, Adolescents, Response, Remission, Prediction

Introduction

Up to one third of patients with schizophrenia have their first symptoms of psychosis before age 18 (Young et al. 2004). Functional impairment occurs most rapidly in the early illness phase and may correlate with a decrease in cerebral gray matter (Buckley et al. 2007). Moreover, the percent of time spent psychotic in the early illness phase predicts future outcome (Harrison et al. 2001). Therefore, reducing time of ineffective treatment is crucial. In this context, early prediction of later response to antipsychotic medication and the time course of response to antipsychotics are of considerable interest (Agid et al. 2003, Correll et al. 2003, Leucht et al. 2007, Leucht et al. 2008, Kinon et al. 2008, Kinon et al. 2010, Ascher-Svanum 2008a). The lack of biomarkers for antipsychotic response (Carbon and Correll, in press) make the use of early response patterns an attractive tool that can be used to guide clinicians in individual decisions regarding the timing of continuation or abortion of an antipsychotic trial in patients with schizophrenia.

Adults with schizophrenia have shown greater symptomatic improvement in the first two weeks of antipsychotic treatment than in subsequent weeks measured as reductions in total scores on the Brief Psychiatric Rating Scale (BPRS, Overall 1974) and Positive and Negative Syndrome Scale (PANSS, Kay 1987) (Agid et al. 2003, Leucht et al. 2005) although symptom improvement might be somewhat slower in patients with a first-episode or recent onset psychosis (Derks et al. 2010, Emsley et al. 2006a, Gallego et al. 2011). A body of evidence has shown that in adults with schizophrenia, lack of noticeable reduction in total BPRS or PANSS scores at week one or two are statistically significant and clinically relevant predictors of later response status (Correll et al. 2003, Leucht et al. 2007, Leucht et al. 2008, Kinon et al. 2008, Kinon et al. 2010, Ascher-Svanum et al. 2008a, Chang et al. 2006, Schennach-Wolff et al. 2010). In addition to predicting greater symptom reduction at study endpoint, several post-hoc analyses have demonstrated that early responders and early non-responders differ also significantly on outcomes not related to the instrument that defines early response/non-response. For example, compared to early non-responders, early responders have had longer time to all-cause treatment discontinuation (Liu-Seifert 2005), lower overall and non-medication related

treatment cost (Ascher-Svanum et al. 2008a), and higher levels of social and physical functioning as measured by the Medical Outcome Survey–Short Form 36 (SF-36) (Ascher-Svanum et al. 2008a).

While the validity and utility of early response/non-response for predicting ultimate outcome has been fairly well established in adults with schizophrenia, much less information is available in pediatric patients. Predicting antipsychotic response in the adolescent population is crucial, as youth with early-onset schizophrenia may have lower response patterns than adults (Sikich et al. 2008) and as adolescents undergo crucial biological, psychosocial and educational maturation processes that need to be disturbed for as short a period as possible to not seriously affect the still all too often unfavorable long-term trajectory of the illness (Clemmensen et al. 2012).

To our knowledge, currently only 2 published studies have examined this issue in adolescents with early-onset schizophrenia (Correll et al. 2013; Stentebjerg-Olesen et al. 2013). In one post-hoc analysis of a large randomized, placebo controlled trial of aripiprazole in 200 adolescents aged 12-17, reduction of PANSS total scores by ≥20% at week 2 and, even more so, at week 3 were significantly predictive of ultimate response status at week 6, defined as a ≥40% total PANSS score reduction (Correll et al. 2013). In the other study, 79 youth aged 6-19 years with schizophrenia (29%) or psychotic disorder not otherwise specified (71%) received naturalistic treatment with clinicians' choice second-generation antipsychotics (77% antipsychotic-naïve). Early response was defined as a Clinical Global Impressions Improvement (CGI-I, Guy, 1976) rating of at least minimally improved at week 4, which significantly predicted ultimate response at week 12, defined as a CGI-I rating of much or very much improved (Stentebjerg-Olesen et al. 2013). These data suggested for the first time that simple and fast CGI-I ratings in the early treatment course could be used in clinical care to identify patients in who treatment will not yield meaningful efficacy, so that antipsychotics could be changed earlier aiming for sparing of ineffective treatments and possibly faster achievement of ultimate response due to earlier treatment switches.

Since most of the adult data on the early response/non-response paradigm is available for olanzapine and risperidone (Leucht et al. 2007, Leucht et al. 2008, Kinon et al. 2008, Kinon et al. 2010, Ascher-Svanum et al. 2008a, Pelayo-Teran et al 2010, Schennach-Wolff et al. 2010, Gallego et al. 2011), we aimed to examine whether in adolescents with schizophrenia treated for 6 weeks with olanzapine 1) the improvement in total psychopathology is also largest in the first two weeks , and 2) early response/non-response defined as a percentage improvement on the BPRS-C total score, are significant predictors of response/non-response and remission/non-remission at study endpoint. Based on the adult data and early findings in adolescents reviewed above, we hypothesized that the early response paradigm and its predictive value would extend to olanzapine and adolescents schizophrenia.

Methods

This study was a post-hoc analysis of data derived from a randomized, placebo-controlled, multisite 6 week double-blind trial comparing olanzapine and placebo in adolescents with schizophrenia (Kryzhanovskaya 2009). A brief description of the parent study is provided below; additional details have been published previously (Kryzhanovskaya 2009).

Study design and participants

The RCT study included 107adolescents aged 13 to 17 years and diagnosed with schizophrenia according to DSM-IV-TR criteria and by interview and assessment with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL, Kaufman 1997). Patients could be either inpatients or outpatients and were recruited from multiple sites in the United States (20 sites) and Russia (5 sites) from November 2002 to April 2005. Patients were required to have a total score of 35 or higher on the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C, Overall 1982), with a score of 3 or higher on at least one of the following BPRS-C items at enrollment and randomization: hallucinations, delusions, or peculiar fantasies.

Eligible patients were randomly assigned in a 2:1 ratio to either olanzapine in flexible doses (2.5-20.0 mg/day) or placebo. Olanzapine was titrated to at least 10.0 mg/day by the third week. Thereafter, investigators were instructed to increase the dose of study medication to the highest tolerated dose, provided there were no tolerability concerns. The present post hoc analyses included only those patients who were allocated to the olanzapine arm and who had at least two post-baseline assessments (at 2 or 3 weeks to assess early response and at least one additional assessment to determine ultimate response).

Efficacy and safety assessments

The primary efficacy measure was the mean change in the BPRS-C total score. Other efficacy outcomes measures included the Positive and Negative Syndrome Scale (PANSS, Kay 1987), the Clinical Global Impressions-Severity Scale (CGI-S, Guy 1976) the Overt Aggression Scale (OAS, Yudofsky 1986) and the Child Health Questionnaire-Parent Form 50 (CHQ-PF50, Landgraf 1996). In addition, changes in the Clinical Global Impressions Improvement Scale (CGI-I, Guy 1976) were evaluated at end-point.

Safety outcomes included frequency of adverse events and changes in body weight and metabolic measures. Extrapyramidal side effects (EPS) were assessed by the Simpson-Angus Scale (SAS, Simpson and Angus 1970), the Barnes Akathisia Scale (BARS, Barnes 1989) and the Abnormal Involuntary Movement Scale (AIMS, Schooler 1982). Tests were performed at protocol-specified time-points, when clinically indicated, and when a patient completed the 6-week study period or discontinued early from the study. Fasting (≥8 hours) glucose and lipids were collected at baseline and endpoint.

Statistical Analysis

The focus of this study was to characterize and predict the trajectory of treatment response in adolescents with schizophrenia treated with olanzapine.

For the purpose of this post-hoc analysis, early response (ER) was defined as a ≥20% reduction in BPRS-C total score at week 2 (ER2) or week 3 (ER3). ENR was defined as a <20% reduction in BPRS-C total score at week 2 (ENR2) or week 3 (ENR3). Ultimate response (UR) was defined as a percent BPRS-C total score reduction at study endpoint (week 6) of ≥20% (UR20), ≥30% (UR30), ≥40% (UR40) or ≥50% (UR50) (last observation carried forward, LOCF). Remission was defined at the end of the double-blind phase (LOCF), using the symptom severity component of the standardized remission criteria (Andreasen 2005), i.e., a score of ≤3 on 7 BPRS-C indicators, including items 4: conceptual disorganization, 7: mannerisms/posturing, 8: grandiosity, 11: suspiciousness, 12: hallucinatory behavior, 15: unusual thought content, and 16: blunted affect. The time criterion (6 months) of the consensus criteria was not be applied owing to the study duration of 6 weeks.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were evaluated to determine the value of ER2/NER2 and ER3/NER3 for predicting presence or absence of ultimate response and remission at week 6. Sensitivity was defined as the proportion of ultimate responders who were correctly classified as early responders at week 2 or 3. Specificity was defined as the proportion of ultimate non-responders who were correctly classified as early non-responders at week 2 or 3. PPV was defined as the proportion of early responders at week 2 or 3 who remained responders at week 6, and NPV was defined as the proportion of early non-responders at week 2 or 3 who remained non-responders at week 6.

ER and ENR groups were compared on different variables using descriptive statistics for patient demographics and baseline characteristics, as well as for the proportionate weekly PANSS-T score change relative to the overall PANSS-T score change. ER and the ENR groups were also compared on the BPRS-C total, PANSS total, CGI-S, CGI-I, OAS, CHQ-PF50 scores and all-cause

discontinuation, using chi squared test or t-test for categorical and continuous variables, respectively. Furthermore, receiver operating characteristic curves (ROC curves) were calculated for ER2 and ER3 regarding the BPRS-C total score reduction (predicting ≥20% , ≥30% , ≥40% or ≥50%) at week 6, to determine the BPRS-C total score improvement threshold at week 2 and week 3 with the best predictive power for ultimate response at week 6.

Finally, stepwise elimination logistic regression models for response and remission (in patients. randomized to olanzapine) were performed using baseline variables only or baseline variables, ER status at week 2 or 3 and EPS post-baseline to examine which demographic, illness and treatment characteristics predicted treatment response (defined a priori as ≥40% reduction in BPRS-C total score) or remission at endpoint.

Although this was a placebo controlled trial, like in prior analyses of early antipsychotic response, we focused on response prediction of patients randomized to olanzapine only; placebo response patterns are the focus of a separate report.

TABLE 1

Results

Patient population

Of 107 adolescents with schizophrenia, randomized to 6 weeks of treatment olanzapine (n=72) or placebo (n=35), 69 patients with at least two follow up visits, one of which included week 2 or week 3 were included in the analyses.

Patient disposition has been described in detail previously (Kryzhanovskaya 2009). Briefly, 49/72 (68.1%) of olanzapine treated patients completed the 6 week double-blind trial. Of the 23 patients

discontinuing early, 10 (13.9%) discontinued due to lack of efficacy and 5 (6.9%) due to adverse events.

Baseline demographic, illness and treatment characteristics are shown in Table 1. The majority of patients were male, white and most had been treated previously with antipsychotics. There were no differences between ENR and ER patients in baseline variables except for more ER3 than ENR3 patients having EPS at baseline (15 (35.7%) vs. 2 (8.7%), p=0.02).

FIGURE 1

Efficacy outcomes

Symptom reduction with olanzapine occurred predominantly early in the first 2 weeks of treatment (figure 1). As early as by the end of week 1, on average 51.1% of the overall improvement was already achieved, with an additional improvement of 22.2% during week 2 (total=73.3%) and 12.2% during week 3 (85.5%).

At week 2, 47/69 patients (68.1%) were ER, and at week 3, 43/66 patients (65.2%) were ER (Table 2). Significantly more patients identified as early responders at 2 or 3 weeks achieved an ultimate response of ≥40% or ≥50% reduction in BPRS-C total score at week 6, i.e., UR40: ER2=66.0% vs. ENR2=13.6%, p<0.001 and ER3=74.4% vs. ENR3=8.7%, p<0.001; UR50: ER2=51.1% vs. ENR2=9.1%, p=0.001 and ER3=60.5% vs. ENR3=0%, p<0.001 (Table 2).

TABLE 2

Compared to ENR2 patients, ER2 patients had significantly greater improvements in BPRS-C total score at every study week (p=0.003 to p<0.001) and LOCF endpoint (-16.6±23.2 vs -50.4±21.2,

p<0.001) (Table 2). Likewise, compared to ENR3 patients, ER3 patients also had significantly greater improvements in BPRS-C total score at every study week and at LOCF end-point (-15.2±20.6 vs. -53.7±20.0, p<0.001). In addition, ER2 and ER3 patients had significantly greater improvements in CGI-S and CGI-I scores compared to ENR2 and ENR3 patients (p=0.047 to <0.001). ER3 patients had significantly greater improvement in OAS score (p=0.02) compared to ENR3 patients whereas the change in OAS score was not significantly different between ER2 and ENR2 patients (p=0.15). The changes in CHQ-PF50 were significantly different between ER and ENR patients (p=0.025 to 0.006), except for the psychosocial summary mean at week 2 (Table 2). Finally, compared to early non-responders, all-cause discontinuation was significantly less likely in ER2 (p=0.047) and ER3 (p=0.018) subjects (Table 2).

Significantly more ER2 than ENR2 patients had remitted at study endpoint (33 (70.2%) vs. 9 (40.9%) p=0.039). The same was true for ER3 compared to ENR3 patients (34 (79.1%) vs. 7 (30.4%), p<0.001).

Predictive value of early response and non-response

The results of the predictive value analyses of an early response of ≥20% reduction in BPRS-C total score at week 2 or week 3 for predicting ultimate response and remission at week 6 are summarized in Table 3. Early response at week 3 generally had slightly better predictive power than early response at week 2 for both ultimate response and remission. The same was true for the prediction of ultimate non-response via presence of early nonresponse. For UR40 and UR50 the specificity (86%-100%) and PPV (91%-100%) were high, while the sensitivity (51%-74%) and NPV (46%-66%) were moderate.

TABLE 3

Regarding the prediction of remission, ER2 and ER3 showed moderate and somewhat lower predictive validity than for UR. Consistent with the findings for UR, values for remission were higher regarding sensitivity (70%-79%) and PPV (79%-83%) than for specificity (59%-70%) and NPV (48%-64%), and ER 3 had the best predictive validity for remission with both sensitivity and PPV of around 80%.

Receiver Operating Characteristic (ROC) Curves to determine the best cutoff for early response/non-response

To find the optimal cut-off threshold of the psychopathological improvement at 2 or 3 weeks to predict response/non-response or remission/non-remission at week 6, ROC-curves were generated for the reduction in BPRS-C total score at week 2 and week 3 (Table 4). At 2 weeks a cut-off threshold of 19.8% reduction to predict ≥20% reduction showed the highest accuracy (accuracy=84%) and the greatest area under the curve (AUC=0.88). At 3 weeks, cut-off thresholds of 20.0% and 38.7% reduction to predict ≥20% and ≥50% reduction respectively, at week 6, showed the highest accuracy (accuracy=83.3%, 84.8%) and the greatest AUC (AUC=0.92, 0.91). Except for the ER3 of 38.7% to predict ≥50% reduction, all other optimal cut-off points for ER2 and ER3 to predict a percentage response at week 6 were around 20% (19.8%-23%). This was also true for remission, where ROC curves showed optimal cut-off points of 16% reduction in BPRS-C total score at week 2 and 20% reduction in BPRS-C total score at week 3 to best predict remission at week 6.

TABLE 4

Predictors of ultimate response and remission

The logistic regression analysis showed that predictors of response (defined as ≥40% reduction in BPRS-C total score) were ER2 ($p=0.0001$), ER3 ($p<0.0001$), a lower baseline AIMS total score (0.041-0.044), a higher baseline SAS total score ($p=0.047$), male gender ($p=0.0075$) and a higher

baseline BPRS-C withdrawal score (p=0.026) (Table 5). Predictors of remission were ER2 (p=0.0044), ER3 (p=0.0003) and a lower baseline CGI-Severity score (p=0.0007-0.0013) (Table 5).

TABLE 5

Adverse effect outcomes

There were no differences in adverse effect outcomes between ER2/ER3 patients and ENR2/ENR3 patients, except for ER3 patients having a greater improvement in EPS assessed by the Simpson-Angus Scale compared to ENR3 patients (p=0.008) (Table 6). Both ER and ENR patients gained body weight over the 6 weeks of treatment and increased mean blood cholesterol, triglycerides and fasting glucose from baseline to end-point. Moreover, around 45% of the patients gained ≥7% of body weight (Table 6).

TABLE 6

Discussion

Main findings from this post hoc analysis of a 6-week randomized, double-blind, placebo-controlled trial of olanzapine vs. placebo for adolescents suffering from schizophrenia include: 1) most of the symptomatic improvement was achieved by weeks 1 and 2; 2) ER and ENR patients did not differ significantly regarding baseline demographic, illness and treatment variables; 3) ER 2 and even more so ER 3 significantly predicted UR and remission; 4) a threshold for ER of ≥20% BPRS-C reduction was confirmed as having the best predictive validity for UR; 5) patients with ER were superior to NER patients on almost all other efficacy outcomes that were independent of the BPRS-C that was used to define ER, while adverse effects did not differ significantly between ER and NER patients; 6) ER2 and ER3 remained significant predictors of UR in multivariable regression analyses that only identified one or two additional clinical predictors.

Our finding that patients achieved most of the symptomatic response early in treatment (51% by week 1, 73% by week 2 and 86% by week 3) is consistent with studies in adults with schizophrenia where the improvement up to week 2 was significantly larger than the additional improvement up to week 4 (Agid et al. 2003, Agid et al. 2006). Moreover, in adults the improvement in the first 4 weeks of treatment was also significantly greater than the additional improvement during the rest of the next 11 months (Agid et al. 2006, Leucht et al. 2005). Similarly, our findings are also consistent with emerging data in adolescents with schizophrenia (Correll et al. 2013) or youth with schizophrenia-spectrum disorders (Stentebjerg-Olesen et al. 2013), in whom most of the symptomatic improvement also occurred in the first 2-4 weeks of a new treatment trial. Nevertheless, the proportional amount of symptomatic response at week 1 was double than seen in a 6-week double blind randomized trail with aripiprazole where at week 1 and 2 was around 25% of the overall PANSS total score reduction was seen (Correll et al. 2013). This difference may be due to more sedating effects of olanzapine or also due to differences in the overall PANSS score reduction from baseline, which was larger in the aripiprazole arms (-31 points) (Findling et al. 2009) than in the olanzapine arm (-21 points) (Kryzhanovskaya et al. 2009) (with parallel differences in the placebo response (-21 and -9 points, respectively).

Confirmation of the early response paradigm in adolescents with schizophrenia strengthens the rationale for examining the utility of presence/absence and degree of early improvement as a clinical biomarker for later non-response. In fact, in line with studies in adults (Correll et al. 2003, Leucht et al. 2007, Leucht et al. 2008, Kinon et al. 2008, Kinon et al. 2010, Ascher-Svanum et al. 2008a, Stauffer et al. 2011, Hatta et al. 2011) and emerging pediatric data (Correll et al. 2013, Stentebjerg-Olesen et al. 2013), we confirmed that early responders at week 2 or 3 had significantly better outcomes across a whole host of efficacy measures. Exceptions were the isolated lack of a difference in the psychosocial summary score of the CHQ-PF50 between ER2/NER2 at week 6, as functional improvement may take longer than 6 weeks, and in adverse effects in this short-term study. Similarly to a study of adolescents with schizophrenia treated with aripiprazole in a 6-week placebo controlled

trial (Correll et al. 2013), early response/non-response status at week 3 was somewhat superior to week 2 in predicting outcomes at week 6.

Similarly to prior work in adults (Leucht et al. 2008) and the common practice in the literature on ER in schizophrenia, we found with the exception of a single outlier (ER3 of 38.7% to predict UR50) that thresholds of around 20% (16%-23%) reduction of BPRS-C total score at week 2 or 3 were the optimal cut-off point for ER to predict UR and remission. Using equipercentile linking, the ≥20% reduction in PANSS (or Brief Psychiatric Rating Scale) scores was found to be comparable to ”minimal improvement” on the CGI-I scale (Leucht 2005b). Since the CGI-I can easily be utilized in busy clinical settings, it should be considered in clinical care, as lack of at least minimal improvement on the CGI-I at week 4 was shown predict UNR at week 12, defined as much or very much improved on the CGI-I in youth with schizophrenia spectrum disorders (Stentebjerg-Olesen 2013).

Using this 20% improvement threshold in BPRS-C total score at week 2 or 3 to define ER or ENR, 65% of the olanzapine treated adolescents with early-onset schizophrenia were categorized as ER. This two third figure for ER status is higher than found in a study of adolescents with early-onset schizophrenia randomized to aripiprazole, where ER2 and ER3 was achieved by 33% and 49%, respectively (Correll et al. 2013). However, the early response frequency of about 65% is also higher than reported in adult studies, where frequencies were 43%-47% in first-episode schizophrenia (Stauffer et al. 2011, Emsley et al. 2006a) and 22-30% in chronic schizophrenia also treated with olanzapine (Ascher-Svanum et al. 2008a, Kinon et al. 2010, Kinon et al. 2008). Reasons for this difference in the proportion of early responders are unclear, but could for example relate to differences in pre-baseline exposure to antipsychotics and degree of required washout, which each will affect pre-baseline response status and baseline severity of psychophathology. Another possibility is that olanzapine and aripiprazole have differing levels and/or time course of efficacy. Nevertheless, these discrepant results require further study through examination of other studies of youth with schizophrenia receiving olanzapine and other antipsychotics, ideally in the same trial.

Further, our results suggest that prediction of UR may be more accurate in adolescents with schizophrenia than prediction of UNR, at least when treated with olanzapine. From a clinical point of view, however, NPV and specificity for prediction of ultimate non-response are the most important variables, since an accurate and early identification of non-responders provides an opportunity of changing ineffective treatment without exposure of patients to ultimately ineffective or suboptimal treatments. For UR 40 and UR 50, the specificity was between 86% and 100%. Thus, most or all of the patients who were ultimate non-responders at week 6 were already early non-responders at week 2 or 3. Nevertheless, while PPV was high (91%-100%), sensitivity (51%-74%) and NPV (46%-66%) were only moderate, indicating that 2 or 3 weeks may not suffice to reliably identify youth with schizophrenia who will not have sufficient benefit from longer treatment with the same antipsychotic. These results are somewhat in line with data from adults with first episode schizophrenia (Emsley et al. 2006a, Gallego et al. 2010) in whom also a longer time until ultimate treatment response was observed than reported in studies with more chronic patients. However, these data contrast with the findings from the study of adolescents with schizophrenia treated with aripiprazole where ER at week 2 and 3 had very favorable NPVs for UR 40 of 81.7% and 93.6% (Correll et al. 2013). Although these discrepant findings could also influenced by different response rates in the two populations, these varying results underscore the need to identify additional clinical and biomarkers of response to antipsychotics in patients with schizophrenia. Moreover, recent work has extended the early antipsychotic response paradigm that dichotomizes the early illness course and uses this to predict UR and remission to examining different trajectories of symptomatic change from baseline to endpoint (Levine and Leucht 2010; Schennach et al. 2012, Nordon et al. 2014, Pelajo-Teran et al. 2014). Other approaches have included trying to identify a smaller number of most predictive individual PANSS items that comprise the early response, rather than using a cut off across ratings of all 30 PANSS items (Ruberg et al. 2010). It remains to be seen how this work can inform individualized clinical decision making in the future.

Finally, using multivariable regression analyses, we confirmed that ER2 and ER3 remained robust and significant predictors of UR and remission, even when entering baseline variables as potential moderators and change in the severity of symptom severity in EOS subjects as potential mediators. In addition, higher BPRS-C withdrawal and baseline SAS scores, lower baseline AIMS scores and male sex predicted response, whereas lower baseline CGI-S score predicted remission. Studies in adults found next to early response higher baseline psychopathology scores to be a predictive of UR, whereas lower baseline psychopathology scores predicted remission at endpoint (Schennach-Wolff et al. 2011a, Crespo-Facorro et al. 2007, Emsley et al. 2006b). In our study, only higher baseline BPRS-C withdrawal scores were associated with greater response in our study, but we also found that patients with less CGI severity, i.e., those closer to remission, were more likely to achieve remission during the 6-week study. The finding that higher baseline SAS scores were associated with a higher likelihood of UR may relate to a change from antipsychotics with higher EPS potential that can interfere with full therapeutic benefits in youth (Stentebjerg-Olesen et al. 2013) and adults (Schennach-Wolf et al. 2011b). Similarly, higher baseline, but not 4-week akathisia ratings were found in subsequently non-remitting first-epsiode schizophrenia subjects (Derks et al. 2010). The finding that lower AIMS baseline scores were associated with achieving UR is consistent with findings in adults with chronic schizophrenia indicating that patients with tadive dyskinesia respond more poorly to antipsychotics (Ascher-Svanum et al. 2008b), possibly indicating a more disturbed dopamine physiology. Finally, although male sex has traditionally been associated with poorer antipsychotic response, recent findings have been more heterogeneous, which may have to do with the time frame of observation. Interestingly, male sex no longer predicted poor treatment outcome in the majority of recent studies that focused on the early post-acute period, whereas studies that confirmed a poorer outcome in males with a first episode of schizophrenia reported mostly on time frames of at least one year (Carbon and Correll – in press).

Strengths and Limitations

Results from this study must be interpreted within its limitations. First, the study was a post-hoc analysis and since the study was a randomized controlled trial, its generalizability to everyday clinical samples may be reduced. Second, we were only able to evaluate early improvement and its predictive validity within the first 6 treatment weeks, whereas prediction of longer-term outcome is also very important. Third, our outcome variables did not extend to subjective well-being or daily functioning at school, work or interpersonally. On the other hand, strengths of this study include the use of standardized assessment instruments, double-blind treatment assignment and symptom ratings, relatively low dropout rate, use of a single antipsychotic and reasonable large sample size of adolescents with early-onset schizophrenia.

Conclusions

Adolescents with schizophrenia treated with olanzapine achieved the majority of symptomatic improvement during the first 1-2 weeks of treatment. Early response at 2 and 3 weeks predicted ultimate response and remission at week 6, with ER3 having the best predictive power. ER patients were more likely to maintain their improvements through the study endpoint, while ENR did not have similarly high predictive power for UNR. A 20% improvement threshold for defining ER was confirmed as a robust measure. ER and ENR should be assessed and considered as valuable information for clinical decision making in youth with early-onset schizophrenia. Additional research is needed to enable more individualized antipsychotics treatment and determination of the best time and circumstance for either continuing an antipsychotic trial in a patient with still insufficient response or aborting the trial and switching to another agent.

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Table 1. Baseline Demographic, Illness and Treatment Characteristics of Olanzapine-Treated Subjects With an ER/ENR at Study Week 2 and of Subjects with an ER/ENR at Study Week 3

	Week 2			**Week 3**		
	Olanzapine (*n=69*)			**Olanzapine (*n=66*)**		
	Early Non-responder (*n = 22*)	**Early Responder (*n = 47*)**	**p- value**	**Early Non-responder (*n = 23*)**	**Early Responder (*n = 43*)**	**p- value**
Age, years, median	16	16	0.66	15	16	0.20
Gender male, n (%)	16 (72.7)	32 (68.1)	0.70	16 (69.6)	31 (72.1)	0.83
Race			0.43			0.99
White, n (%)	17 (77.3)	32 (68.1)		16 (69.6)	30 (69.8)	
Non-White, n (%)	5 (22.7)	15 (31.9)		7 (30.4)	13 (30.2)	
Country, n (%)			0.92			0.35
Russia	10 (45.4)	22 (46.8)		9 (39.1)	22 (51.2)	
USA	12 (54.6)	25 (23.2)		14 (60.9)	21 (48.8)	
BMI, kg/m^2, median	23.2	21.6	0.32	23.3	21.5	0.22
Illness characteristics						
Illness duration, years, median	3.5	2	0.60	2	2	0.91
Age at onset, years, median	13	14	0.72	13	14	0.39
Onset before age 13, n (%)	14 (63.6)	31 (66.0)	0.85	14 (60.9)	30 (69.8)	0.47
Schizophrenia first degree relative, unknown/yes n (%)	6 (27.3)	11 (23.4)	0.73	6 (26.1)	9 (20.9)	0.63
Schizophrenia second degree relative, unknown/yes n (%)	9 (40.9)	22 (46.8)	0.65	9 (39.1)	20 (46.5)	0.56
Axis I history first degree relative, unknown/yes n (%)	7 (31.8)	18 (38.3)	0.60	8 (34.8)	14 (32.6)	0.86
BPRS-C Total score, mean (SD)	49.6(10.7)	50.3(9.8)	0.79	51.1 (11.6)	49.8 (9.4)	0.63
PANSS Total, mean (SD)	93.0 (13.5)	96.1 (14.7)	0.40	96.0 (14.3)	94.7 (14.9)	0.74

CHQ-PF50 psychosocial*, mean (SD)	24.5 (13.1)	25.6 (11.0)	0.81	23.8 (13.1)	25.1 (10.3)	0.76
CHQ-PF50 physical*, median	55.6	52.5	0.24	54.8	51.7	0.27
CGI-S			0.44			0.70
= 4, n (%)	10 (45.5)	14 (29.8)		8 (34.8)	15 (34.9)	
= 5, n (%)	9 (40.9)	25 (53.2)		10 (43.5)	22 (51.2)	
= 6, n (%)	3 (13.6)	8 (17.0)		5 (21.7)	6 (13.9)	
mean (SD)	4.7 (0.7)	4.9 (0.7)		4.7 (0.8)	4.8 (0.7)	
OAS Total score >0 n (%)	7 (31.8)	23 (48.9)	0.18	8 (34.8)	20 (46.5)	0.36
Simpson-Angus Total Score >0, n (%)	3 (13.6)	14 (30.4)	0.23	2 (8.7)	15 (35.7)	**0.02**
Barnes Total Score >0, n (%)	6 (27.3)	14 (30.4)	0.79	8 (34.8)	10 (23.8)	0.34
AIMS Total Score >0, n (%)	2 (9.1)	7 (15.2)	0.25	4 (17.4)	5 (11.9)	0.71
Treatment characteristics						
Olanzapine, mean modal dose (median)	10	12.5	0.43	10	12.5	0.65
Olanzapine, mean maximum dose (median)	15	15	0.43	15	12.5	0.09

*US subjects only; bolded p-value: $p<0.05$.

Patients with an early response showed a ≥20% reduction from baseline in BPRS-C Total score.

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BMI, body mass index; BPRS-C, Brief Psychiatric Rating Scale- Children; CHQ-PF50, Child Health Questionnaire Parent Form 50; CGI-S, Clinical Global Impression – Severity; ER, early response; ENR, early non-response; OAS, Overt Aggression Scale; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation

Table 2. Summary of Efficacy Related Outcomes Assessed at Week 6 (LOCF) in Olanzapine-Treated Subjects by ER2 versus ENR2 or by ER3 versus ENR3.

Outcome	Week 2 – ER			Week 3 – ER		
	Early Non-responder (*n = 22*)	**Early Responder (*n = 47*)**	***p* value**	**Early Non-responder (*n = 23*)**	**Early Responder (*n = 43*)**	***p* value**
BPRS-C Total score, % change, mean (SD)	-16.6 (23.2)	-50.4 (21.2)	**<0.001**	-15.2 (20.6)	-53.7 (20.0)	**<0.001**
Remission, n (%)	9 (40.9)	33 (70.2)	**0.039**	7 (30.4)	34 (79.1)	**<0.001**
Ultimate BPRS-C reduction ≥ 20%, n (%)	9 (40.9)	45 (95.7)	**<0.001**	10 (43.5)	42 (97.7)	**<0.001**
Ultimate BPRS-C reduction ≥ 30%, n (%)	6 (27.3)	36 (76.6)	**<0.001**	5 (21.7)	36 (83.7)	**<0.001**
Ultimate BPRS-C reduction ≥ 40%, n (%)	3 (13.6)	31 (66.0)	**<0.001**	2 (8.7)	32 (74.4)	**<0.001**
Ultimate BPRS-C reduction ≥ 50%, n (%)	2 (9.1)	24 (51.1)	**0.001**	0 (0.0)	26 (60.5)	**<0.001**
CGI-S change, mean (SD)	-0.6 (0.8)	-1.4 (0.9)	**0.001**	-0.5 (0.6)	-1.5 (0.9)	**<0.001**
CGI-I change, mean (SD)	-0.6 (1.4)	-1.3 (1.2)	**0.047**	-0.4 (1.2)	-1.5 (1.1)	**<0.001**
OAS Total change, mean (SD)	0.3 (2.0)	1.2 (3.1)	0.15	-0.3 (3.1)	1.5 (2.6)	**0.02**
CHQ-PF50* point change psychosocial summary, mean (SD)	-6.5 (9.3)	-12.5 (13.8)	0.19	-4.5 (9.2)	-16.4 (12.5)	**0.006**
Physical summary, mean (SD)	11.1 (11.1)	2.5 (6.2)	**0.025**	9.1 (10.5)	2.2 (6.2)	**0.042**
All-cause discontinuation, n (%)	10 (45.5)	9 (19.1)	**0.047**	10 (43.5)	6 (14.0)	**0.018**

* US Subjects only; bolded p-value: $p<0.05$.

Abbreviations: BPRS-C, Brief Psychiatric Rating Scale – Children; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; CHQ-PF50, Child Health Questionnaire Parent Form 50; ER, early response; LOCF, last observation carried forward; OAS, Overt Aggression Scale

Table 3. Predictive Value of Early Response for Ultimate Response to Olanzapine Defined By Different Percent Score Reductions at Study Endpoint (Week 6 LOCF)

	Accuracy in predicting a BPRS-C Total score reduction at endpoint								**Accuracy in predicting remission at endpoint**	
	Early response – Week 2				**Early response – Week 3**				**ER – Week 2**	**ER – Week 3**
Predictive value for UR	**≥20% ***	**≥30% ***	**≥40% ***	**≥50% ***	**≥20% ***	**≥30% ***	**≥40% ***	**≥50% ***		
Sensitivity (%)	96	77	66	51	98	84	74	60	70	79
Specificity (%)	59	73	86	91	57	78	91	100	59	70
PPV (%)	83	86	91	92	81	88	94	100	79	83
NPV (%)	87	59	54	46	93	72	66	58	48	64

*Reduction in BPRS-C Total score.

Abbreviations: BPRS-C, Brief Psychiatric Rating Scale-Children; ER, early response; LOCF, last observation carried forward; NPV, negative predictive value; PPV, positive predictive value; UR, ultimate response

Table 4. Receiver Operating Characteristic Curve-Derived Best Cut Off Scores for Defining Early Response as a Predictor of Ultimate Response to Olanzapine Defined By Different Percent BPRS Score Reductions of at Study Endpoint (Week 6 LOCF)

	ER ROC Threshold	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**AUC**	**Lower 95% CI**	**Upper 95% CI**
Early Response at Week 2									
Ultimate Response:									
≥20% BPRS ↓	19.8%	0.833	0.867	0.957	0.591	0.841	0.877	0.777	0.976
≥30% BPRS ↓	23.0%	0.786	0.704	0.805	0.679	0.754	0.792	0.680	0.904
≥40% BPRS ↓	23.0%	0.882	0.686	0.732	0.857	0.783	0.829	0.735	0.924
≥50% BPRS ↓	23.0%	0.923	0.605	0.585	0.929	0.725	0.810	0.709	0.910
Early Response at Week 3									
Ultimate Response:									
≥20% BPRS ↓	20.0%	0.808	0.929	0.977	0.565	0.833	0.918	0.847	0.989
≥30% BPRS ↓	21.6%	0.878	0.760	0.857	0.792	0.833	0.864	0.773	0.956
≥40% BPRS ↓	21.6%	0.941	0.688	0.762	0.917	0.818	0.887	0.810	0.963
≥50% BPRS ↓	38.7%	0.808	0.875	0.808	0.875	0.848	0.914	0.848	0.979

CI, confidence interval; ER, early response; NPV, negative predictive value; PPV, positive predictive value; ROC, Receiver Operating Characteristic; AUC, Area under the Curve; BPRS, Brief Psychiatric Rating Scale

Table 5. Stepwise Elimination Logistic Regression Models for Response and Remission using Baseline Variables only or Baseline Variables and Early Response Status at Week 2 or 3 Plus Extrapyramidal Side Effects Post Baseline

Models	**Response: ≥ 40% Reduction in BPRS-C Total Score**			**Remission** [a]		
	Significant Variables	p- Value	r square	**Significant Variables**	p- Value	r squared
1. Baseline Variables only						
	Overall Model	0.013	0.116	*Overall Model*	0.0003	0.163
	Lower Baseline AIMS Total Score	0.044		Lower Baseline CGI Severity Score	0.0013	
	Higher Baseline SAS Total Score	0.047				
2. Baseline Variables plus Early Response at Week 2 and SAS >0 post baseline						
	Overall Model	< 0.0001	0.336	*Overall Model*	< 0.0001	0.259
	Early Response [b] at Week 2	0.0001		Lower Baseline CGI Severity Score	0.0007	
	Male Gender	0.0075		Early Response [b] at Week 2	0.0044	
	Lower Baseline AIMS Total Score	0.041				
3. Baseline Variables plus Early Response at Week 3 and SAS >0 post baseline						
	Overall Model	< 0.0001	0.409	*Overall Model*	< 0.0001	0.369
	Early Response [b] at Week 3	< 0.0001		Early Response [b] at Week 3	0.0003	
	Higher Baseline BPRS-C	0.026		Lower Baseline CGI Severity	0.0009	

	withdrawal			Score		

AIMS: Abnormal Involuntary Movement Scale; BPRS-C: Brief Psychiatric Rating Scale-Child Version; SAS: Simpson-Angus Rating Scale

[a] Remission: defined cross-sectionally as a score of ≤3 (mild or less) on the following eight PANSS items at the end of the study (LOCF after week 2 assessment), using the cross-sectional remission criteria by Andreasen *et al* (Andreasen *et al,* 2005): P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), G9 (unusual thought content), G5 (mannerisms/posturing), N1 (blunted affect), N4 (social withdrawal), and N6 (lack of spontaneity/flow of conversation)

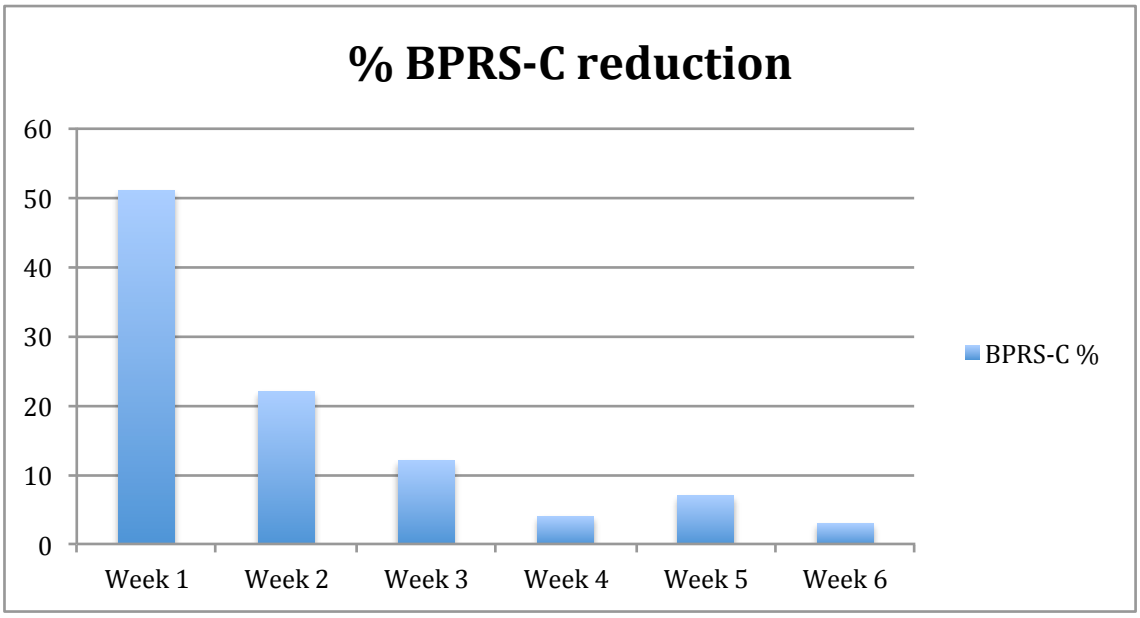
[b] Early Response: defined as at least a 20% reduction in BPRS-C

Table 6. Adverse Effects during the 6-Week Trial in Subjects Treated with Olanzapine Achieving Either ER2/ENR2 or ER3/ENR3

Outcome	ENR2 (*n* = 22)	ER2 (*n* = 46)	p- value	ENR3 (*n* = 23)	ER3 (*n* = 42)	p- value
Mean change from baseline in:						
Total cholesterol (mmol/l), mean (SE)	0.06 (0.03)	0.09 (0.02)	0.46	0.06 (0.03)	0.10 (0.02)	0.39
Change in triglycerides (mmol/l), mean (SE)	0.48 (0.19)	0.55 (0.13)	0.75	0.79 (0.19)	0.41 (0.13)	0.11
Change in fasting glucose (mmol/l), mean (SE)	0.07 (0.03)	0.02 (0.02)	0.20	0.03 (0.03)	0.04 (0.02)	0.83
Change in body weight (kg), mean (SE)	4.0 (2.9)	5.0 (4.2)	0.31	4.4 (2.6)	5.3 (4.1)	0.35
Change in body weight (%), mean (SE)	6.2 (1.3)	7.6 (0.9)	0.38	6.7 (1.2)	8.1 (0.9)	0.37
Weight gain ≥7%, n (%)	7 (31.8)	24 (52.2)	0.22	9 (39.1)	22 (52.4)	0.50
Change in BMI z-score, mean (SE)	0.3 (0.1)	0.4 (0.1)	0.49	0.3 (0.1)	0.4 (0.1)	0.31
Mean change from baseline in:						
Simpson-Angus Scale total score	0.1 (0.8)	-0.3 (1.8)	0.14	0.4 (0.8)	-0.5 (1.7)	**0.008**
Barnes Akathisia Scale total score	0.6 (2.0)	0.5 (2.0)	0.83	0.4 (2.2)	0.5 (2.0)	0.94
AIMS total score	0.2 (1.1)	0.5 (1.7)	0.33	0.5 (1.8)	0.4 (1.5)	0.73
Simpson-Angus Scale total score >0, n (%)	3 (13.6)	14 (29.8)	0.23	6 (26.1)	10 (23.3)	1.0
Barnes Akathisia Scale total score >0, n (%)	2 (9.1)	8 (17.0)	0.48	4 (17.4)	5 (11.6)	0.71
AIMS total score >0, n (%)	1 (4.6)	9 (12.8)	0.42	1 (4.4)	6 (14.0)	0.41

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; ENR, early non-response; ER, early response

Figure 1. Weekly Percent BPRS-C reduction from baseline to endpoint (LOCF)



LOCF: last observation carried forward

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Information on PhD student:	
Name of PhD student	Marie Stentebjerg-Olesen
E-mail	mso@dadlnet.dk
Date of birth	260671
Work place	Mental Health Centre of Copenhagen
Principal supervisor	Pia Jeppesen

Title of PhD thesis:
Investigation of the early response as predictor of clinically significant effects of antipsychotics in children and adolescents with psychosis

This declaration concerns the following article:
Early Response/Nonresponse at week 2 or 3 predicts ultimate response/nonresponse in adolescents with schizophrenia treated with olanzapine: resluts from a 6-week randomized, placebo-controlled trial

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Signature of the co-authors:			
Date:	**Name:**	**Title:**	**Signature:**
10/28/14	Christoph Correll	Professor of Psychiatry	Christoph Correll
10/11/14	PIA JEPPESEN	Ass prof. phd.	Pia Jeppesen

Signature of the PhD student and the principal supervisor:	
Date: 10/11-14	**Date:** 10/11-14
PhD student:	**Principal supervisor:** Pia Jeppesen

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Information on PhD student:	
Name of PhD student	Marie Stentebjerg-Olesen
E-mail	mso@dadlnet.dk
Date of birth	260671
Work place	*Mental Health Centre of Copenhagen*
Principal supervisor	Pia Jeppesen

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Signature of the co-authors:			
Date:	Name:	Title:	Signature:
10/11-14	Mauricio Tohé	Professor	

Signature of the PhD student and the principal supervisor:	
Date: 10/11-14	Date: 10/11-14
PhD student:	Principal supervisor: Pte Teppese

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Signature of the co-authors:			
Date:	**Name:**	**Title:**	**Signature:**
10/13/14	Melissa DelBello, MD	Professor of Psychiatry and Pediatrics	

Signature of the PhD student and the principal supervisor:	
Date: 10/11-14	**Date:** 10/11-14
PhD student:	**Principal supervisor:** Per Jeppesen

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Information on PhD student:	
Name of PhD student	Marie Stentebjerg-Olesen
E-mail	mso@dadlnet.dk
Date of birth	260671
Work place	Mental Health Centre of Copenhagen
Principal supervisor	Pia Jeppesen

Title of PhD thesis:
Investigation of the early response as predictor of clinically significant effects of antipsychotics in children and adolescents with psychosis

This declaration concerns the following article:
Early Response/Nonresponse at week 2 or 3 predicts ultimate response/nonresponse in adolescents with schizophrenia treated with olanzapine: resluts from a 6-week randomized, placebo-controlled trial

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	**(A,B,C)**
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2. Planning of the experiments and methodology design, including selection of methods and method development	A
3. Involvement in the experimental work	A
4. Presentation, interpretation and discussion in a journal article format of obtained data	B

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Signature of the co-authors:			
Date:	**Name:**	**Title:**	**Signature:**
10/11/2014	Stephen J. Ganocy, PhD	Assistant Professor	Stephen J. Ganocy

Signature of the PhD student and the principal supervisor:	
Date: 10/11-14	**Date:** 10/11-14
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Signature of the co-authors:

Date:	Name:	Title:	Signature:
Oct 13, 2014	Robert Findling	MD	

Signature of the PhD student and the principal supervisor:

Date: 10/11-14	**Date:** 10/11 - 14
PhD student:	**Principal supervisor:** Pia Jeppesen

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Date:	**Name:**	**Title:**	**Signature:**
16-10-2014	Anne Katrine Pagsberg	MD PhD	
20-10-14	PIA JEPPESEN	MD PhD	Pia Jeppe

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Date: 10/11-14	**Date:** 10/11-14
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Date:	**Name:**	**Title:**	**Signature:**
10/28/14	Christoph Correll	Professor of Psychiatry	

Signature of the PhD student and the principal supervisor:	
Date: 10/11-14	**Date:** 10/11-14
PhD student:	**Principal supervisor:**

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Date:	Name:	Title:	Signature:
21/10-14	Anders Finn-Jensen	Professor	Anders Finn-Jensen

Signature of the PhD student and the principal supervisor:	
Date: 10/11-14	Date: 10/11-14
PhD student:	Principal supervisor: Pic Jeppesen

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Signature of the co-authors:

Date:	Name:	Title:	Signature:
10/28/14	Aseel Al-Jadiri	pediatric Resident	

Signature of the PhD student and the principal supervisor:

Date: 10/28/2014	Date: 10/11-14
PhD student: Aseel Al-Jadiri, MD 10/11-14	Principal supervisor: Pic Jeppesen

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	Pagsberg, Anne Katrine,		
	Fink-Jensen, Anders	7/10 - 2014	Anders Fink-Jensen

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Signature of the co-authors:

Date:	Name:	Title:	Signature:
10/21/14	Sandeep Kapoor, MD	Director, SBIRT (North Shore Long Island Jewish HEalth System)	

Signature of the PhD student and the principal supervisor:

Date: 10/11-14	Date: 10/11-14
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Date:	**Name:**	**Title:**	**Signature:**
20.10.14	Maren Carbon-Correll	Dr. med	Maren Carbon-Correll

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B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

Signature of the co-authors:			
Date:	**Name:**	**Title:**	**Signature:**
10/28/14	Correll, Christoph U.	Professor of Psychiatry	

Signature of the PhD student and the principal supervisor:	
Date: 10/11-14 **PhD student:**	**Date:** 10/11-14 **Principal supervisor:** Pia Jeppesen

DECLARATION OF CO-AUTHORSHIP

About this form

- Declarations of co-authorship must be included in your PhD thesis if your thesis contains or is based on co-authored manuscripts or published articles.
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Information on PhD student:	
Name of PhD student	Marie Stentebjerg-Olesen
E-mail	mso@dadlnet.dk
Date of birth	260671
Work place	Mental Health Centre Copenhagen
Principal supervisor	Pia Jeppesen

Title of PhD thesis:
Investigation of the early response as predictor of clinically significant effects of antipsychotics in children and adolescents with psychosis

This declaration concerns the following article:
Early nonresponse determined by the clinical global impressions scale predicts poorer outcomes in youth with schizophrenia spectrum disorders naturalistically treated with second-generation antipsychotics.

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	**(A,B,C)**
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B

2. Planning of the experiments and methodology design, including selection of methods and method development	A
3. Involvement in the experimental work	A
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	***Has contributed to the co-operation***	***0-33 %***
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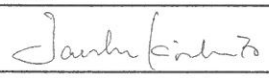
Signature of the co-authors:			
Date:	**Name:**	**Title:**	**Signature:**
22/10/2014	Taishiro Kishimoto	MD	

Signature of the PhD student and the principal supervisor:	
Date: 10/11-14	**Date:** 10/11-14
PhD student: 	**Principal supervisor:**