



Treatment of early onset schizophrenia: recent trends, challenges and future considerations

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Early onset schizophrenia (onset before adulthood) is a rare, severe, and chronic form of schizophrenia. The clinical presentation of schizophrenia at this unusually early age of onset has been associated with premorbid developmental abnormalities, poor response to neuroleptic treatment, greater admission rates, and poor prognosis. This is a brief, condensed review of current treatment strategies for the early onset population highlighting the need for novel treatment strategies for these generally treatment-refractory cases. Based on the current literature, second-generation antipsychotics remain the mainstay of treatment, although current medications provide suboptimal response at best. Based on the adult literature, combining antipsychotic treatment with psychotherapeutic intervention may be a more comprehensive treatment strategy. Indeed, early detection, identification of relevant biomarkers, coupled with advancing knowledge of the neurochemical and neuroanatomic pathways may help design informed and novel treatment strategies.

Keywords: adolescent, antipsychotic, schizophrenia, MEG, early intervention

Schizophrenia is a complex psychiatric disorder afflicting 1% of the population worldwide. The neurodevelopmental model of schizophrenia posits that the pathophysiology can be traced in the early stages of development (Weinberger, 1987; Rapoport et al., 1997; Gogtay et al., 2011). Adolescent onset schizophrenia is less common and phenotypically more severe. The very early onset form of this debilitating disorder (childhood onset schizophrenia; onset of psychosis before age 13) is exceedingly rare, much more severe, may be homogeneous, with a chronic, treatment-refractory course (Childs and Scriver, 1986; Sporn et al., 2007). For this review, both are jointly referred to as early onset schizophrenia (EOS). The early forms are both phenotypically and neurobiologically continuous with the adult-onset illness (Jacobsen and Rapoport, 1998; Hollis, 2000), though EOS patients show greater neurodevelopmental impairments early in life such as delay in language/speech, linguistic ability, motor coordination, and poor psychosocial functioning (Asarnow et al., 1994; Caplan, 1994; Nicolson and Rapoport, 1999; Nicolson et al., 2000; McClellan and Werry, 2001; McClellan et al., 2003; Fleischhaker et al., 2005; Gornick et al., 2005; Vyas et al., 2007).

The clinical severity and early age at onset in EOS results in long-term use of antipsychotic medication as a mainstay of treatment, coupled with psychotherapeutic intervention. Increasingly, efforts are being made toward early detection and management of prodromal symptoms, which may make it possible to implement early preventative and treatment strategies before the onset of the syndromal illness. The use of medication (or treatment in general) at the prodromal stage, however, has also resulted in challenging clinical and ethical issues. Therefore, the identification of novel and evidence-based treatment interventions that effectively improve symptomatology and outcome in EOS is warranted. We discuss issues relating to prodromal intervention, followed by a selective review on pharmacological treatment and

psychotherapeutic interventions mostly focusing on EOS. It is assumed that both treatment modalities are part of a comprehensive treatment plan, involving an initial assessment of the patient, awareness of the child's developmental stage, and understanding of the family system perspective.

EARLY DETECTION AND MANAGEMENT OF PSYCHOSIS

Adolescence is a period of profound changes in the brain structure with a complex interplay between biological, psychological, and social factors. Mental health problems commonly emerge in adolescence and many adolescents have enduring disorders rather than simply a transient "teenage" emotional turmoil. Individuals who develop psychosis often experience a prodromal phase (also known as "at-risk mental state"), which typically involves changes in perception, behavior, cognition, mood, and physiology (Yung and McGorry, 1996; McGorry et al., 2001). This phase is ambiguous because of the non-specificity of symptoms that are commonly observed during development in adolescence, and the low predictive power in identifying individuals who make a transition to psychosis (McGorry and Killackey, 2002). Structured instruments, such as Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2001), Scale of Prodromal Symptoms (SOPS; Miller et al., 1999), the Bonn Scale for the Assessment of Basic Symptoms (BSABS; Gross et al., 1987), the Personal Assessment and Crisis Evaluation (PACE; Phillips et al., 2002), and the Comprehensive Assessment of At Risk Mental States (CAARMS; Yung et al., 2004), can help better characterize the prodromal phase although these lack "predictive" value. In recent years, better characterization of the prodrome phase of the disorder and improved prediction algorithms have shown to be effective in informing the timing and management process of early intervention (Cadenhead et al., 2010). In the PACE study, Yung et al. (2004) conducted a 12-month follow-up on individuals with ultra high-risk, proposing

a “four-or-more” algorithm for risk identification, including poor functioning, long duration of symptoms, high levels of depression, and reduced attention. The algorithm showed a positive predictive value of 80%, with heightened specificity and sensitivity values (Yung et al., 2004). In the North American Prodrome Longitudinal Study (NAPLS) cohort, Cannon et al. (2008) followed up 291 treatment-seeking patients with prodromal symptoms at regular intervals for up to 2.5 years. The study showed conversion rates to be 35% at follow-up, with baseline characteristics predictive of psychosis to include a genetic predisposition of schizophrenia alongside reduced overall functioning, heightened levels of abnormal thought content, greater psychosocial impairment, and a history of substance abuse (Cannon et al., 2008). Similar findings have been reported in the European Prediction of Psychosis (EPOS) study (Ruhrmann et al., 2010). However, there is a paucity of “biomarkers” for this phase with good predictive value either for course or treatment response. Although the identification of biomarkers for schizophrenia is in its early stages, some attempts have been made to discover biomarkers in EOS (Taurines et al., 2010; Micó et al., 2011). There is limited evidence that management and symptom specific treatment of help-seeking prodromal patients may delay or prevent the onset of psychosis; however the uncertainty of course prediction adds to the risk of stigmatization and heightened anxiety in individuals and their families. Additionally, the EOS cases tend to be insidious, non-episodic, and typically result in rapid deterioration; providing a limited chance to study and intervene during this window.

The identification of biomarkers would improve the ability to intervene during the prodromal period or earlier. The search for clinically relevant biomarkers is a challenging task in a heterogeneous disorder like schizophrenia but studying EOS provides a unique opportunity as the phenotype is relatively homogenous, associated with less risk of secondary influences from disease associated alterations of environment (e.g., marijuana, smoking, hospital admissions, etc.) and typically shows more salient genetic loading (Vyas et al., 2010, 2011a). Adult studies have attempted to identify putative biomarkers. For example, a neurocognitive deficits in schizophrenia is considered a core feature of the illness (meta-analysis, Heinrichs and Zakzanis, 1998; Heaton et al., 2001; Keefe and Fenton, 2007) and studies on ultra high-risk cohorts suggest that impairments in olfactory identification and spatial working memory (measures targeting the dorsolateral prefrontal cortex and cortical physiological processes), may have a strong predictive value for conversion to psychosis (Brewer et al., 2006). Neurophysiological measures such as electroencephalography, event-related potentials, prepulse inhibition, and mismatch negativity, also show promise as potential biomarkers (Javitt et al., 2008; Wiedemann, 2011; Vyas et al., 2012) but further work to elucidate the relationship of such measures with specific clinical expression (e.g., negative symptoms, cognitive functioning) is needed. Neuroimaging studies have shown relatively less predictive value despite consistent reports of progressive structural brain abnormalities associated with schizophrenia (Gogtay et al., 2004; Rapoport and Gogtay, 2011), and non-psychotic siblings of COS patients (Gogtay et al., 2003; Greenstein et al., 2011). Some studies have suggested that high-risk individuals that go on to become psychotic show less gray matter volume in the right medial temporal,

lateral temporal, inferior frontal cortex, and in the cingulate cortex bilaterally, while individuals who do not develop psychosis show changes restricted to the cerebellum (Pantelis et al., 2003). Such observations should be strengthened further with multimodal neuroimaging.

PHARMACOLOGICAL TREATMENT IN EOS

There is a relative dearth of evidence-based studies of antipsychotic (both typical and atypical) efficacy in EOS, partly because of the rarity of the population and partly because it is difficult to do treatment trials in children with severe illness (Gogtay and Rapoport, 2008). Taken together, these studies suggest that although first-generation antipsychotics (FGAs) improve positive symptomatology, they elicit significant extra pyramidal side effects, tardive dyskinesia, and prolactin elevations (Pool et al., 1976; Realmuto et al., 1984; Spencer et al., 1992; Findling et al., 1998). As a result, second-generation antipsychotics (SGA, or atypical antipsychotics) have become the mainstay of therapy in the treatment of EOS, because of their potential for lower propensity to induce extrapyramidal symptoms and reduced risk of tardive dyskinesia (Madaan et al., 2008; Masi and Liboni, 2011). However the Cochrane review identified 6 (clinical trials) studies with a total of 256 children and adolescents, to examine the effects of antipsychotic medication for EOS (Kennedy et al., 2007). The SGA used for comparisons were clozapine, risperidone, and olanzapine. The authors concluded that there was limited data that supported one antipsychotic medication over another for the treatment of EOS. There was no superiority of SGAs over FGAs, given the evidence showing small differences in effect size for alleviating positive and negative symptoms. Furthermore, an 8-week, government-funded, randomized double-blind trial on EOS entitled “Treatment of Early-Onset Schizophrenia Spectrum” (TEOSS) showed that SGAs, risperidone and olanzapine, were not superior to FGA, molindone, in symptom improvement. Risperidone and olanzapine were associated with high degrees of weight gain (risperidone additionally showed elevated prolactin concentration) in comparison with molindone, while individuals prescribed to molindone showed akathisia (Sikich et al., 2008).

Clozapine remains the gold standard treatment for schizophrenia, and has been shown to have a more favorable profile of clinical response compared with haloperidol and olanzapine in treatment-refractory EOS (Spencer et al., 1992; Mozes et al., 1994; Towbin et al., 1994; Kumra et al., 1996, 2008; McEvoy et al., 2006). However, clozapine remains as the last resort choice limited by its significant side effect profile on the hematopoietic system (agranulocytosis), cardiovascular system (myocarditis), central nervous system (seizures, akinesia, myoclonic jerks), and liver function, along with other side effects such as severe movement disorders, hypersalivation, hyperglycemia, diabetes, and weight gain, which are particularly problematic for children and young adults (Connor et al., 2001; Vyas et al., 2011b).

Clearly, there is an ongoing debate about the efficacy of atypical medications accounting for the long-term side effects profile, and therefore there is a pressing need for larger randomized control trials (RCTs), to delineate the best available antipsychotic agents, and provide a platform for novel drug discovery.

PSYCHOTHERAPEUTIC INTERVENTIONS

To date, there are no published RCTs of psychosocial treatments for children with schizophrenia. However, the adult literature has supported adjunct psychosocial and individualized psychological treatments (Eack et al., 2009; review, Vyas et al., 2012). A review concluded that psychosocial therapies (cognitive behavioral therapy, CBT), family intervention, social skills training, and cognitive remediation) are effective adjuncts to pharmacological interventions in adults with schizophrenia (McGurk et al., 2007; Patterson and Leewenkamp, 2008). For example, CBT addresses dysfunctional beliefs, coping strategies, “tuning” of cognitive abilities, and behavior modification, by linking and then re-evaluating thoughts and feelings about the presentation of clinical symptoms, which in turn aims to improve the mental states of patients. Cognitive enhancement therapy has also shown to be effective in improving neurocognitive functioning in outpatients with EOS or schizoaffective disorder (Eack et al., 2009). Indeed, family therapy, psycho-education, and social skills training have also shown improvement in clinical symptoms of newly diagnosed patients with schizophrenia (Petersen et al., 2005). A recently published multicenter RCT was conducted on young people with an early initial prodromal state of psychosis, to investigate the effectiveness of integrated psychological intervention (including CBT, group skills training, cognitive remediation therapy, and multifamily psycho-education) and supportive counseling on prevention of psychosis (Bechdolf et al., 2012). The results showed that the integrated psychological intervention was more effective in delaying the onset of psychosis over a 24-month follow-up period (Bechdolf et al., 2012). These studies suggest that psychotherapeutic interventions may thus be an important platform to alleviate psychotic relapse, re-admission, and medication compliance; systematic validation of such measures however is warranted.

CONCLUSION AND FUTURE DIRECTIONS

Early onset schizophrenia is a rare, severe, and treatment-refractory form of the adult-onset illness. Although antipsychotic treatment, in addition to psychotherapeutic interventions, provides some symptom relief, there are a very high percentage of residual psychotic symptoms and cognitive deficits. Existing

medication treatments do not result in adequate response and the side effects in children remain daunting. Hence, there is a dire need for early characterization of symptoms and biomarkers, better understanding of the pathophysiology and progression of the illness, and exploring novel and “outside the box” treatment options such as transcranial magnetic stimulation (TMS; Tanaka and Watanabe, 2009), or transcranial direct current stimulation (tDCS) trials, which are well tolerated in pediatric populations (Mattai et al., 2011; Vercammen et al., 2011). Non-invasive neurostimulation techniques such as these have been shown to ameliorate cognition and negative symptoms in schizophrenia (Levkovitz et al., 2011; Minzenberg and Carter, 2012), features commonly reported in early onset cases (Vyas et al., 2011a). However, new treatment strategies should be informed by advancing knowledge from neurochemical and neuroanatomic studies, which may provide more specific targets in the brain. Recent advances in neuroimaging methodologies, particularly those that provide a window into brain functioning and circuitry, may provide a blueprint for identification of novel biomarkers for schizophrenia. For instance, resting-state and task orientated functional MRI or magnetoencephalography (MEG) analyses show abnormal brain synchrony and neural networks in schizophrenia (Reite et al., 1999; Banaschewski and Brandeis, 2007; Ford et al., 2007; Brookes et al., 2011; Ikezawa et al., 2011). An ongoing MEG study from our NIMH COS cohort showed abnormal oscillatory patterns in COS patients compared to healthy controls (N. S. Vyas, unpublished data). Treatment strategies could be ideally designed (e.g., regionally specific neuromodulation using tDCS) to “normalize” these abnormal brain circuitries or evaluate efficacy of new compounds. Research and implementation of novel treatments coupled with advances in genome-wide microarray technology may lead to the identification of genes that are relevant not only in the pathophysiology of schizophrenia, but also in providing an insight into treatment response, or course prediction.

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