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Practitioner Review: Psychosis in Children and Adolescents

Anna Sunshine[1], **Jon McClellan**[1]

[1]Department of Psychiatry, University of Washington, Seattle, WA, USA.

Abstract

Psychotic symptoms, including hallucinations, delusions and disorganized thinking and behaviors, are the hallmarks of schizophrenia; but may also present in the context of other psychiatric and medical conditions. Many children and adolescents describe psychotic-like experiences, which can be associated with other types of psychopathology and past experiences (e.g., trauma, substance use, suicidality). However, most youth reporting such experiences do not have, nor will ever develop, schizophrenia or another psychotic disorder. Accurate assessment is critical, because these different presentations have different diagnostic and treatment implications. For this review, we focus primarily on the diagnosis and treatment of early onset schizophrenia. In addition, we review the development of community-based first-episode psychosis programming, and the importance of early intervention and coordinated care.

Introduction

Psychosis, defined by impaired reality testing and disruptions in thinking, perceptions and behavior, presents in the context of many different neuropsychiatric and medical conditions. Both historically, and based on current DSM and ICD nosology, psychotic syndromes are narrowly defined, with diagnoses based on overt symptoms, characteristic patterns and course of illness, and clear evidence of impairment (e.g, schizophrenia). Over the past two decades, there has been a substantial increase in research and program development addressing premorbid and subclinical psychotic states, with the goal of identifying individuals at-risk or in the early stages of developing schizophrenia or other psychotic disorders (McIlwaine and Shah, 2021). One of the drivers for this movement is the recognition that there have been at best incremental advancements in therapeutics for schizophrenia since the discovery of chlorpromazine, and that early intervention with both medication and psychosocial treatments, has the potential to ameliorate morbidity and mortality.

As a result, numerous clinical trials and community networks of care have been developed to address individuals at-risk or experiencing first episode psychosis (McGorry, Mei, Hartmann, and Nelson, 2021). While these efforts are promising, the accuracy of predicting which individuals reporting subthreshold or attenuated symptoms will eventually develop a psychotic disorder (such as schizophrenia) remains a challenge (Lieberman, Small and Girgis, 2019).

In this discussion, it is important to recognize that efforts to identify and intervene early with psychotic illnesses have potentially broadened how psychosis is conceptualized.

Epidemiological studies find that substantial numbers of youth and adults report psychotic-like experiences (Kelleher et al., 2012). Although a primary goal of early psychosis programs is to improve the prognosis of severe psychotic illnesses, most individuals enrolled in these programs have brief or transient psychosis, and do not go on to develop schizophrenia or a psychotic mood disorder (Fusar-Poli et a., 2016). How broad is the spectrum of psychosis, and how best to define psychotic illnesses (and reported experiences suggestive of psychosis), are ongoing debates.

Given that schizophrenia specifically, and psychotic disorders in general, are markedly heterogeneous, some argue that the diagnostic nosology should shift to a broader rubric of psychosis spectrum (Guloksuz and van Os, 2018). In addition to addressing the wide range of psychotic (and psychotic-like) symptoms reported in clinical and epidemiological samples, classifying these varied presentations under the single entity of psychosis spectrum could potentially reduce stigma and demoralization associated with the diagnostic and prognostic implications of schizophrenia.

Whether this is a valid approach remains to be seen. In the history of medical science, expanding diagnostic heterogeneity has generally hampered efforts to identify specific biological causes, a necessary step for advancing treatment development and personalized medicine. While it is true that schizophrenia and other psychotic conditions are characterized by extreme heterogeneity, grouping all conditions and suspected presentations into one category will exacerbate, not solve the problem. Further, diagnosing a child with psychosis based solely on subjective symptom reports, without other corroborating clinical evidence, increases the risk of inaccurate diagnosis and exposure to unnecessary treatments (particularly antipsychotic medications). In child psychiatry, the controversies regarding “pediatric bipolar disorder” provide some cautionary lessons (Carlson, 2022).

In this review, we suggest that distinguishing between psychotic-like experiences, psychotic symptoms and specific psychotic disorders is key to effective treatment. Therefore, we will first address the differential diagnosis of disorders that can be accompanied by psychotic symptoms, with the primarily focus on the diagnosis and treatment of early onset schizophrenia.

Early Onset Schizophrenia

Early onset and childhood onset schizophrenia (EOS and COS respectively) are diagnosed using the same DSM-5 or ICD-11 criteria used to diagnose the disorder in adults. By convention, COS is defined as onset before age 13 years; EOS is defined as onset before age 18 years. Schizophrenia generally first presents during middle to late adolescence, with an overall population prevalence of approximately 0.7% (McGrath, Saha, Chant, and Welham, 2008). Onset during childhood is rare, with the prevalence of COS estimated at 0.0025% (Gochman, Miller, and Rapoport, 2011). Early onset is often associated with negative symptoms, cognitive deficits, and premorbid problems, all of which predict greater long-term morbidity and impairment (AACAP, 2013). With early effective treatment, most individuals improve, and in some cases the symptoms remit, although most affected persons need long-term treatment.

To diagnose schizophrenia, both DSM-5 (American Psychiatric Association, 2013) and ICD-11 (World Health Organization, 2018) require some combination of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. DSM-5 requires evidence of the illness for at least 6 months duration, whereas ICD-11 only requires one month of persistent symptoms to make the diagnosis.

Clinical Course

Individuals who develop schizophrenia often have significant premorbid social and cognitive difficulties (AACAP, 2013). Prior to the onset of psychosis, the patient typically experiences prodromal symptoms, defined by changes in thinking and behavior such as odd beliefs, attenuated psychotic symptoms, and deteriorations in social, academic and self-care functioning. Prodromal periods can range in length from days to weeks to a more insidious onset. Distinguishing between a suspected prodrome and more commonplace adolescent problems, such as anxiety, depression and substance use, remains a challenge and may contribute to delayed diagnosis.

During the acute phase of illness, affected individuals present with overt mental status changes, including hallucinations, delusions, bizarre behaviors and impairment in functioning (AACAP, 2013). With the resolution of acute positive symptoms, patients often experience ongoing difficulties with negative symptoms and dysphoria. Some individuals will recover from their episodes completely, whereas others suffer chronic long-term impairment, often due to residual negative symptoms. Unfortunately, psychotic symptoms do not remit in all patients, despite adequate treatment, resulting in chronic impairment.

Diagnostic Assessment

A comprehensive evaluation, sometimes requiring multiple and longitudinal assessments, is needed to accurately diagnose schizophrenia and other psychotic disorders. Standardized diagnostic assessments, including the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL DSM-5 November 2016) (Kaufman, Birmaher, Axelson, Perepletchikova, Brent, and Ryan, 2016) and the Structured Clinical Interview for DSM, Childhood Version (KID SCID) (Hien et al., 1994), help improve accuracy. Symptom questionnaires for assessing psychotic symptoms and monitoring treatment response include the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein and Opler, 1987) and the Brief Psychiatric Rating Scale for Children (BPRS-C) (Hughes, Rintelmann, Emslie, Lopez and MacCabe, 2001)

Establishing the validity of symptom reports suggestive of psychosis is important. Many children and adolescents (an estimated 17% and 8%, respectively) report psychotic-like symptoms (Kelleher et al., 2012), including descriptions of possible hallucinations and odd beliefs. The majority of children and adolescents reporting such experiences do not have a psychotic disorder (nor will they develop one), although they are at risk for other mental health problems (Rimvall et al., 2019; Kırlı et al. 2019). The endorsement of hallucinations and other subjective experiences is not sufficient to diagnose psychosis, and needs to be assessed in the context of clinical presentation, history and objective changes in mental state and behavior (McClellan, 2018).

Once it is determined that the patient is experiencing psychosis, the next step is to identify the underlying cause. Psychotic symptoms are the key features of schizophrenia spectrum disorders, but also occur with mood disorders and other medical conditions (AACAP, 2013). Effective treatment depends upon accurate diagnosis. Misdiagnosis is common early in the course of illness as clinical presentations often shift and evolve over time (Castro-Fornieles et al., 2011; Bromet et al., 2011).

Differential Diagnosis

Bipolar Disorder: Differentiating between bipolar disorder and schizophrenia spectrum disorders can be a challenge, especially during the early course of the illness (Bromet et al., 2011). Psychotic symptoms in mania often involve florid delusions and elaborate thought, versus the paucity of speech and thought characteristic of schizophrenia (AACAP, 2013). Mania is not typically associated with negative symptoms (although differentiating depression and negative symptoms can be a challenge). Markedly decreased sleep is a hallmark of mania, but disrupted sleep also occurs with schizophrenia. Family psychiatric history may be informative.

Major Depression with psychotic features: Although some studies report a high rate of psychosis associated with major depression in children and adolescents (Ryan et al., 1987), epidemiological studies find that the risk increases with age (Jääskeläinen et al., 2018). The pediatric literature is confounded by difficulties in distinguishing true psychosis that occurs solely in the context of mood disorders, versus nonspecific reports of psychotic-like experiences, which have less clear clinical significance and are more generally associated with histories of dysphoria, suicidal behaviors and trauma (Hlastala and McClellan, 2005).

Schizoaffective disorder: Schizoaffective disorder is diagnosed when core features of schizophrenia and major mood episodes are both present over the course of illness. However, given the overlap and variability in symptom presentation over time, the diagnosis is unreliable in clinical settings (Malaspina et al., 2013).

Substance-induced disorders: Drugs associated with psychosis include cocaine, cannabis, amphetamines, inhalants, hallucinogens and synthetic recreational drugs (Wilson, Szigeti, Kearney and Clarke, 2018). Daily use of high potency cannabis is associated with higher rates of first episode psychosis (Di Forti et al., 2019). Young people with substance-induced psychosis share clinical risk factors and illness characteristics with those who have schizophrenia, and many eventually are diagnosed with a primary psychotic illness (O'Connell, Sunwoo, McGorry and O'Donoghue, 2019). Because substance use is common in individuals with psychotic disorders and psychotic-like experiences, establishing whether substances are causative or contributing agents is difficult. For younger children accidental ingestion of recreational substances and medications that can induce psychosis (e.g. steroids, antiepileptics, dextromethorphan, antibiotics) should also be considered.

Trauma: Children and adolescents who report psychotic-like experiences have higher rates of exposure to trauma and symptoms of PTSD (Kelleher et al., 2013). In the absence of

more overt signs of thought disorganization, bizarre behaviors or a compelling prodromal course, reports of atypical psychotic experiences in young people are more often associated with childhood maltreatment (Hlastala and McClellan, 2005) and features of borderline personality disorder (Sengutta, Gawęda, Moritz, and Karow, 2019). A trauma history does not preclude a diagnosis of schizophrenia, but it is important to distinguish psychosis from post-traumatic phenomena as the approaches to treatment are different.

Developmental Disorders and Autism: Symptoms of autism, including lack of social and emotional reciprocity, restricted fixated interests and perseverative idiosyncratic beliefs, can sometimes mirror negative symptoms and disordered thinking in schizophrenia. The course of illness, and presence or absence of positive symptoms, are key to the differential diagnosis. Core features of autism represent long-standing baseline patterns of language, interests and behavior; whereas the onset of schizophrenia represents a marked deviation from the person's baseline level of functioning (Larson et al., 2017).

Distinguishing these patterns can be a challenge in persons with baseline developmental problems that worsen during adolescence. Children with autism spectrum disorder are at higher risk for developing psychotic symptoms (Sullivan, Rai, Golding, Zammit and Steer, 2013), and youth with schizophrenia have high rates of premorbid difficulties consistent with autism spectrum (Rapoport, Giedd and Gogtay, 2012). Both conditions stem from early disruptions in neurodevelopment, and some genetic errors are associated with both illnesses (Rapoport et al., 2012). To make the diagnosis of schizophrenia in a person with autism, prominent hallucinations or delusions must be present.

Medical conditions: Medical conditions, including medication toxicity, delirium, central nervous system infections, endocrine and metabolic disturbances, autoimmune disorders, genetic syndromes, and neoplasms, are potential causes of psychosis (Staal, Panis and Schieveld, 2019). In general, other than substance-induced psychosis, most medical illnesses associated with psychosis are rare. Clinical indicators, such as physical exam findings, response to antipsychotic treatment, severity, time course of functional decline, and exposure history, should guide the extensiveness of the workup (AACAP, 2013). The diagnostic evaluation (e.g. laboratory tests, lumbar puncture, EEG, MRI) must be tailored based on symptom presentation and history to avoid overly intrusive/expensive testing (Staal, Panis and Schieveld, 2019). Of recent attention, autoimmune encephalitis, including anti-NMDAR encephalitis, is a rare potential cause of pediatric psychosis. Serum autoantibody testing should be considered in cases where psychosis is preceded by a flu-like prodrome and/or accompanied by neurological symptoms including catatonia (Sarkis, Coffey, Cooper, Hassan, and Lennox, 2019).

First-episode psychosis

The shift towards the study and treatment of first-episode psychosis has expanded access to specialized community treatment resources for individuals with new onset of a psychotic disorder. However, the focus on first-episode psychosis can capture individuals whose psychiatric diagnosis is ambiguous. In a meta-analytic review of 42 studies including first-episode psychosis assessments and follow-up (total n = 14,484), individuals diagnosed

with schizophrenia spectrum disorders and affective psychoses (29 percent total) were far outnumbered by persons diagnosed with transient or brief psychotic states (65 percent) (Fusar-Poli et al., 2016). Diagnostic stability in individuals with schizophrenia and affective psychoses was relatively high, whereas those with other conditions (transient or brief psychosis, substance induced psychosis, unspecified psychosis) had a much more variable course. Thus, in this literature, first-episode psychosis does not necessarily equate to a diagnosis of schizophrenia or other chronic psychotic conditions.

Racial and cultural issues

Cultural and racial factors influence the diagnosis, assessment and treatment of psychiatric symptoms (Keepers et al., 2020). For example, Black and Hispanic individuals are more likely to be diagnosed with psychotic illnesses than White individuals (Schwartz and Blankenship, 2014). These discrepancies are potentially due to bias in interpreting symptoms and differential access to health care. Structural racism may also contribute to the increased risk of schizophrenia in communities experiencing historical and ongoing discrimination (Misra et al., 2022).

Geographic variability in the reported incidence of schizophrenia may reflect variable environmental risk factors or reveal systematic differences in diagnosis and/or publishing biases (McGrath, Saha, Chant, and Welham, 2008). Differences in schizophrenia prevalence between sites and cultures is also complicated by the reported increased risk for psychosis in people immigrating to another country, particularly for those experiencing social disadvantage (Tarricone et al., 2021). Studies supporting an increased risk of schizophrenia in immigrant communities have primarily been carried out in England and Northern Europe where the vast majority of non-White individuals are either first or second-generation immigrants making it difficult to disentangle the separate effects of perceived race and immigration status on schizophrenia risk (Kirkbride et al., 2012; Kirkbride et al., 2017a; Kirkbride et al., 2017b; Saha et al., 2005; Cantor-Graae et al., 2005). In response to this literature, a small US-based study demonstrated an increased rate of schizophrenia in US-born African Americans that was partially mediated by family socioeconomic status (Bresnahan et al., 2007). Broadly, the interactions between race, historical and structural discrimination and immigration patterns are complex and the relationship between these factors and risk of schizophrenia is likely contextual and multidetermined.

Potential psychotic symptoms must be also assessed in the context of cultural or religious belief systems. For example, in South African Xhosa communities, bewitchment is a commonly held explanation for misfortune (Campbell et al., 2017). Such beliefs can be mistaken for delusions, or alternatively, can influence the content of delusions in persons suffering from a psychotic illness. Cultural consultation may be helpful for better understanding the context of unfamiliar belief systems, and distinguishing a delusion from shared beliefs.

Treatment

For this section, we will focus on the treatment of children and adolescents with a schizophrenia spectrum disorder or those identified as being high risk for developing

schizophrenia. As emphasized in the preceding sections, many underlying conditions can lead children and adolescents to report experiences suggestive of hallucinations and delusions. Careful history and exam findings are critical to differentiate schizophrenia spectrum disorders (and related prodromal symptoms) from other causes (e.g. substance use, PTSD, borderline personality disorder, bipolar disorder). While a probable diagnosis can often be reached after initial assessment, clinical presentations often shift over time. Clinicians should discuss with the individual and family about the risks and benefits of initiating early treatment versus watchful waiting.

The treatment of early onset schizophrenia requires the combination of psychosocial interventions and psychopharmacology (AACAP, 2013; NICE, 2016). Antipsychotic medications target positive psychotic symptoms (e.g., hallucinations, delusions, thought disorder, disorganized behaviors), whereas psychosocial interventions address associated morbidity and functional deficits, including efforts to improve social interactions, self-care and relapse prevention.

Psychopharmacology

Antipsychotic medications are a mainstay of treatment for schizophrenia (Keepers et al., 2020). Randomized controlled trials generally support the efficacy of newer atypical antipsychotics (e.g., risperidone, aripiprazole, olanzapine, paliperidone, lurasidone) and some traditional neuroleptics (e.g., haloperidol, loxapine) in children and adolescents with schizophrenia-spectrum disorders (Krause et al., 2018). However, trials of ziprasidone (Findling et al., 2013) and asenapine (Findling et al., 2015) were not superior to placebo in reducing symptoms of schizophrenia in adolescents. Clozapine is the only agent with evidence of superiority in comparative trials (Krause et al., 2018), but is reserved for treatment resistant cases due to its side effect profile.

Worldwide, risperidone, quetiapine and aripiprazole are the mostly widely prescribed antipsychotic agents in the pediatric population (Hálfdánarson et al., 2017). The choice of which agent to use first is typically based on side effect profile, patient and family preference, clinician familiarity and cost. It is best to start with a medication with evidence of efficacy in the pediatric population, with the exception of olanzapine (given the risk for weight gain) and clozapine. Agents that have not been systemically studied in EOS or those with negative trials (e.g., asenapine, ziprasidone) are best avoided until pediatric data support their use.

Regardless of medication choice, many patients do not remain on the same medication long-term, either due to lack of efficacy, side effects or noncompliance (Findling et al. 2010). If insufficient effects are evident after a therapeutic trial, a different antipsychotic agent should be tried. A therapeutic trial is generally defined as 4 – 6 weeks, using up to FDA approved dosages for adults (with allowances for children less than 13 years of age) as tolerated (AACAP, 2013). However, patients who have a minimal response after 2 weeks on a therapeutic dose are unlikely to respond, and an alternative agent should be considered (Keepers et al., 2020).

Long-acting injectable antipsychotics are helpful for patients with poor medication adherence, and have been shown in studies of adults to reduce rates of hospitalization and relapse (Ostuzzi et al., 2021). While there is some evidence that long-acting injectable agents are helpful for individuals early in their course of illness (Subotnik et al., 2015), they have not been systematically studied in the pediatric population.

Most youth with schizophrenia need long-term treatment, and are at significant risk to relapse if their antipsychotic medication is discontinued (AACAP, 2013). Systematic follow up is needed to monitor symptom response, side effects, and adherence. Medication burden should be reassessed over time, with the goal of maintaining effective dosages while minimizing side effects. After a prolonged remission, some patients may be able to discontinue antipsychotic medications without reemergence of psychosis (Kishi et al., 2019). In these situations, periodic longitudinal monitoring is still recommended given that some individuals whose symptoms remit may eventually experience another psychotic episode.

Antipsychotic Medication Safety

Antipsychotic medications are associated with a number of potential adverse effects, including sedation, weight gain, metabolic problems and extra-pyramidal side effects (Keepers et al., 2020). Although side effect profiles overlap, newer agents are generally more prone to cause weight gain and metabolic problems, whereas traditional neuroleptics are more often associated with extrapyramidal symptoms (EPS). The risks of side effects with long-lasting consequences (e.g. metabolic changes, tardive dyskinesia), emphasizes the importance of accurate diagnosis before prescribing antipsychotics to children and adolescents. As in adult populations, the benefit of the medication needs to be recurrently weighed against not only immediate side effects but also the potential for long-term health consequences.

In a meta-analytic review of antipsychotic trials for EOS (Krause et al., 2018), clozapine, olanzapine and quetiapine were associated with the greatest degree of weight gain. Routine monitoring should include periodic assessment of BMI, fasting glucose, fasting lipid profile, hemoglobin A1C and blood pressure. Clinically significant abnormalities (e.g., hypercholesterolemia) may require referral for specialty care. Psychoeducation regarding healthy lifestyle habits, including cessation of smoking, healthy diet and routine exercise, is recommended for all patients prescribed antipsychotic agents (Keepers et al., 2020). However, in the IMPACT trial (Correll et al., 2020), for youth with antipsychotic-associated weight gain, switching to a different antipsychotic agent with lower metabolic risk, or adding metformin was associated with a significant reduction in BMI, whereas healthy lifestyle education was not effective.

Extrapyramidal side effects, including dystonia, akathisia, tardive dyskinesia and neuroleptic malignant syndrome, can occur with either typical or atypical antipsychotics, and need to be systematically assessed throughout treatment (Keepers et al., 2020). Standardized measures, such as the Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health, 1985), and the Neurological Rating Scale (NRS) (Simpson and Angus, 1970), are helpful for monitoring abnormal movements and neurological side effects. Prophylactic

antiparkinsonian agents can be used to avoid acute EPS, especially in patients at risk that have a previous history of dystonic reactions.

Other potential adverse events noted with antipsychotic agents include sedation, orthostatic hypotension, sexual dysfunction, hyperprolactinemia, elevated liver transaminases and steatohepatitis (Keepers et al., 2020). Electrocardiogram monitoring is recommended when using agents associated with QTc prolongation (e.g., ziprasidone). Clozapine has a more serious potential side effect profile, including the risk of seizures and neutropenia. When using clozapine, established protocols for blood count monitoring must be followed, based on regulatory requirements that vary across different countries (Nielsen et al., 2016).

Adjunctive Medication Treatments

The evidence base supporting the use of concomitant medications to treat comorbid or related problems in schizophrenia is limited in adults (Keepers et al., 2020) and mostly lacking in youth (AACAP, 2013). In clinical practice, adjunctive agents are commonly used, including antiparkinsonian agents (extrapyramidal side effects), β-blockers (akathisia), mood stabilizers (mood instability, aggression), antidepressants (depression, negative symptoms, obsessive-compulsive symptoms) and/or benzodiazepines (anxiety, insomnia, akathisia, catatonia) (Keepers et al., 2020). Medication trials should be conducted systematically to avoid unnecessary polypharmacy.

Psychosocial Treatments

Psychoeducational, supportive, vocational and family interventions are all important components of treatment (NICE, 2016). The goals of treatment include symptom reduction, improving social/occupational functioning, enhancing quality of life and reducing risk for relapse. In adults, treatments supported by research include cognitive-behavioral therapy for psychosis, cognitive remediation, social skills training, assertive community treatment, psychoeducation and family support (McDonagh et al. 2022; Keepers et al., 2020).

To date there are only a few studies of psychological treatment for psychosis in youth, and the evidence of benefit is equivocal (Datta, Daruvala and Kumar, 2020). Interventions that have been studied include cognitive behavioral therapy, cognitive remediation therapy, psychoeducational programs and family interventions (Datta et al., 2020; NICE, 2016). In cognitive behavioral therapy for psychosis (CBTp) therapists use strategies to ameliorate distress from hallucinations/delusions and improve function: therapists work with clients to set achievable goals, normalize the experience of psychosis, and use a curious/data-gathering stance to explore hallucinations/delusions (Morrison and Barratt, 2010). Cognitive remediation therapy (CRT) involves approximately 40 one-hour teaching/therapy sessions where clients complete tasks to improve abilities including verbal memory, problem solving and processing speed (Datta, Daruvala and Kumar, 2020). Efforts are underway to compare the effects of antipsychotic medication, psychological intervention or combination therapy (Morrison et al., 2021).

Coordinated specialty care

Coordinated specialty care is an innovative model of treatment for first episode psychosis designed for community-wide interventions. One example, the NAVIGATE program, is a team-based treatment that combines evidence-based medication management, family therapy, personal therapy and education/employment support and is organized around patient definitions of recovery and a stress-vulnerability concept of psychosis. In adolescents and young adults, NAVIGATE was shown to improve quality of life, increase employment/education engagement and reduce symptoms associated with schizophrenia, as compared with community care (Kane et al., 2015). The program was also effective in reducing racial and ethnic disparities in symptom severity and treatment response (Oluwoye et al., 2018).

High-risk for psychosis

Approximately one-quarter of youth characterized as high-risk, defined by attenuated or brief subthreshold psychotic symptoms and familial risk, progress to psychosis after 36 months (or longer) follow-up. Intervention trials report positive benefits with cognitive behavioral therapy, family treatment, cognitive remediation, antipsychotic and antidepressant medications and omega-3 fatty acid supplementation; however at this point there is not definitive evidence to support specific interventions for the prevention of psychosis in high-risk youth (Catalan et al., 2020).

Precision Medicine

The use of genetic and molecular profiling to guide patient assessment and treatment represents a promising tool for psychiatric therapeutics. As actionable genetic risk factors are identified, the ability to accurately identify disease entities, predict disease course and use effective treatments will improve. However, extreme etiologic heterogeneity, both genetic and environmental, underlying complex psychiatric disease is a major challenge (McClellan and King, 2010).

There are an increasing number of genetic testing strategies available to detect different classes of potential disease-causing mutations, including karyotyping (large chromosomal errors), chromosomal microarray (pathogenic duplications and deletions), gene panels (targeted sequencing to detect established disease-causing mutations), whole exome sequencing (single base pair mutations and small insertions and deletions in coding regions) and whole genome sequencing (single base pair mutations and small insertions and deletions genome-wide) (Hoehe and Morris-Rosendahl, 2018). In psychiatry, genetic testing is currently most useful for individuals with autism and neurodevelopmental disorders. For example, one study detected pathogenic mutations in 12% of toddlers diagnosed with ASD (total n = 299), with specific clinical care recommendations indicated for 72% of those found to have causal events (Harris, Sideridis, Barbaresi and Harstad, 2020). For schizophrenia, the best current evidence for clinical relevance are tests for copy-number errors: for example, the 22q11 deletion (velocardiofacial syndrome) confers a substantial risk for psychotic and neurodevelopmental disorders (Hoehe and Morris-Rosendahl, 2018). The detection of such causal events is important for genetic counseling, and also may identify other types of necessary medical evaluations (e.g., cardiac assessment).

Although pharmacogenomics has been aggressively marketed, with promises of streamlined treatment choice, avoidance of adverse effects and improved clinical outcomes; the utility of pharmacogenetic testing has not been established for routine clinical care in psychiatry (Hoehe and Morris-Rosendahl, 2018). At this time, pharmacogenetic testing should be limited to variants with established clinical relevance (e.g., the HLA-B*1502 allele and the risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in persons of Asian ancestry), as well as potentially in patients with repeated intolerance to medications and/or treatment failure.

In the future, whole-genome sequencing strategies will likely become a routine part of a psychiatric assessment. As risk genes and variants are identified, genotyping strategies potentially will help predict the risk of developing a psychotic illness, as well as identify more specific neurobiological targets for intervention strategies. Since most affected individuals harbor unique risk and moderating factors, research will need to establish connections between individual genotypes and a variety of phenotypes (e.g. specific diagnosis, clinical presentation, response and side effects to treatments). Further, since individuals with schizophrenia have a reduced life expectancy based in part on medical co-morbidities (Keepers et al., 2020), it is possible that some of the risk for medical co-morbidities is due to that same genetic risk factors leading to schizophrenia. The identification of such genetic risk factors could lead to specific health monitoring or treatment options.

Summary

Schizophrenia with onset during late childhood or adolescence is a serious neurodevelopmental disorder that requires long-term treatment and psychosocial support. Accurate diagnosis is key, since most youth reporting psychotic-like symptoms do not have a psychotic disorder and have different treatment needs.

Effective treatment for schizophrenia spectrum disorders includes antipsychotic medication plus educational, supportive and psychotherapeutic interventions. For individuals deemed at risk for psychosis, educational and psychotherapeutic interventions (e.g, CBT and family treatments) are generally recommended before starting medications. Models of coordinated specialty care designed to address first-episode psychosis combine evidence-based pharmacology, psychotherapy, psychoeducation and assertive case management services into community-wide interventions. Further work is needed to broadly disseminate and integrate coordinated care and evidence-based intervention strategies into community systems of care.

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