Schizophrenia in children and adolescents: Treatment overview

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INTRODUCTION

Schizophrenia in children and adolescents is a syndrome consisting of positive and negative symptoms of psychosis that impact development, psychosocial, and cognitive functioning. The etiology of this syndrome is poorly understood, but early diagnosis and treatment are critical to limit the morbidity of the disorder.

Childhood-onset schizophrenia (onset prior to age 13) usually represents a more severe form of the disorder than early-onset (onset between 13 to 18 years) or adult-onset schizophrenia (onset after age 18). It is associated with more prominent prepsychotic developmental disorders, structural brain abnormalities, and genetic risk factors [1-4]. (See "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis", section on 'Terminology'.)

Repeated or prolonged psychotic episodes have deleterious neuropsychological, neurophysiological, and brain structural effects on patients who have been diagnosed with a first psychosis [5-9]. Additionally, evidence suggests that prolonged periods of untreated psychosis may result in increased resistance to conventional treatments [10,11].

This topic reviews our approach to selecting treatments for and subsequent pharmacologic management of schizophrenia in children and adolescents. The clinical manifestations and diagnosis of schizophrenia and the psychosocial treatment of schizophrenia in children and

adolescents are reviewed separately. Topics related to schizophrenia in adults are also reviewed separately.

- (See "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Psychosocial interventions for schizophrenia in children and adolescents".)
- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)
- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)

TREATMENT MODALITIES

Antipsychotic medication is the cornerstone of treatment for schizophrenia and our first line of treatment for schizophrenia in youths. We augment pharmacologic management with psychosocial treatment in all cases when possible.

Antipsychotic medications — Antipsychotic medications include first- and second-generation medications. The mechanism of action for most first- and second-generation medications is postsynaptic blockade of brain dopamine D2 receptors. A comprehensive discussion of first- and second-generation medications including pharmacokinetics, initiation, titration, maintenance, and side effect management is discussed elsewhere. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

Second-generation antipsychotics — Randomized clinical trials have shown several second-generation antipsychotics (with the exception of ziprasidone [12]) to reduce positive and negative symptoms of schizophrenia in youth in comparison with placebo:

- Aripiprazole [13-15]
- Brexpiprazole [16]
- Clozapine [17]
- Lurasidone [18]
- Olanzapine [19]
- Quetiapine [20]
- Risperidone [20]

Adverse effects associated with second-generation antipsychotics include metabolic side effects (weight gain, diabetes, hyperlipidemia), QT interval prolongation, akathisia, acute dystonic

reactions, hyperprolactinemia (risperidone), and tardive dyskinesia. Some of these medications also cause extrapyramidal symptoms but generally at rates lower than first-generation agents. Lurasidone is the least likely to cause metabolic side effects [21] and clozapine has additional side effects such as agranulocytosis. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

First-generation antipsychotics — Few first-generation antipsychotics currently in clinical use have directly been shown to be efficacious for symptoms of schizophrenia in youth. Those that have been shown to be efficacious in clinical trials are listed below:

- Chlorpromazine [22]
- Haloperidol [23,24]
- Loxapine [24]

  Perphenazine, while not tested in clinical trials of youth with schizophrenia, is also used in this population based on our and other clinicians' experience in youth as well as results from efficacy studies in adults [25,26].

Common adverse effects of first-generation antipsychotics include extrapyramidal symptoms (tremor, bradykinesia, shuffling gait, akathisia), acute dystonic reactions, tardive dyskinesia, hyperprolactinemia, and for some agents, QT interval prolongation. First-generation antipsychotic use in adults is reviewed separately. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

Pharmacotherapy in youths — Children and adolescents, compared with adults, are at higher risk of many of the side effects associated with antipsychotic use, including extrapyramidal symptoms, withdrawal dyskinesias, elevated prolactin, weight gain, and metabolic abnormalities [27-31]. Tardive dyskinesias are less common in youth compared with adult and older adult populations (0.4 versus 6.8 percent) [27-32]. The risk of tardive dyskinesia in children appears to be greatest with first-generation antipsychotics with minimal or no risk seen with second-generation antipsychotics, although some of these data are extrapolated from adult studies [27]. (See "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications" and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Metabolic dysregulation' and "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis".)

Psychosocial treatment — Along with pharmacologic therapy, we typically provide psychoeducation, cognitive-behavioral therapy, cognitive enhancement exercises, and educational/vocational skills training and support to all children and adolescents with schizophrenia. Additionally, we advise providing cognitive remediation and social skills training

to individuals with clinically significant deficits in these areas if this treatment is available in the community. These interventions are described separately. (See "Psychosocial interventions for schizophrenia in children and adolescents", section on 'Psychosocial interventions'.)

The availability of these psychosocial interventions varies widely internationally and in the United States. They are more likely to be available in a metropolitan area with an academic medical center, rather than in rural areas.

Clinical trials testing the efficacy of these interventions in children with schizophrenia are largely absent or limited [33-37]. In our clinical experience, we have found them to be helpful in improving adherence and slowing deterioration. Evidence of effectiveness is more robust in adults with schizophrenia. There are no clinical trials comparing different interventions individually or in different combinations. (See "Psychosocial interventions for schizophrenia in children and adolescents", section on 'Psychosocial interventions' and "Schizophrenia in adults: Psychosocial management".)

PRIOR TO INITIATING TREATMENT WITH ANTIPSYCHOTIC MEDICATION

Treatment setting — We treat all children or adolescents in the least restrictive environment where the safety of the individual can be maintained. While ambulatory management is typically preferred, in cases where the individual presents as a risk to themselves or others due to their symptoms (eg, suicidal, homicidal, agitation, unable to care for themselves or have their daily needs met by caregiver) inpatient treatment is indicated.

We assess for the clinically appropriate setting at our initial visit and all subsequent visits with the individual. (See "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis", section on 'Assessment'.)

Baseline testing — Prior to starting treatment with an antipsychotic medication, we obtain baseline complete blood count, metabolic panel including fasting glucose, cholesterol, HgbA1c, waist and hip circumference, baseline weight, and triglycerides. We use these as a baseline and monitor periodically. (See 'Monitoring symptoms and adverse medication effects' below.)

We obtain an electrocardiogram in patients with a family history of arrhythmia or prolonged QT syndrome. Several first- and second-generation antipsychotics are associated with prolonged QT-interval and we would choose to avoid these in these individuals. (See 'Choosing an antipsychotic medication' below and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'QTc interval prolongation and

sudden death' and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects", section on 'QT interval prolongation and sudden death'.)

Further discussion of baseline testing and administration of first- and second-generation antipsychotics can be found elsewhere. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Adverse effects' and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects", section on 'Side effects'.)

Choosing an antipsychotic medication — Our preference is to begin pharmacologic management with a second-generation antipsychotic in children and adolescents with schizophrenia. We base this on their lower rate of extrapyramidal symptoms and tardive dyskinesia compared with first-generation antipsychotics [38,39]. We base our choice of the specific second-generation agent by the clinical features of the individual (eg, agitation, mood symptoms, weight sensitivity), properties of the antipsychotic, and past response to the agent.

- **For individuals with high sensitivity to weight gain or metabolic syndrome** – For individuals with concerns of weight gain or metabolic syndrome, our preference is to treat with lurasidone while avoiding medications with higher rates of metabolic syndrome or weight gain, such as olanzapine [40]. In an adolescent with concerns of weight gain, we would use lurasidone starting at 40 mg and titrating to therapeutic range. We would then monitor prior to further increases in medication. Aripiprazole would be another option for this clinical scenario. (See 'Starting and titrating antipsychotics' below.)

  In a six-week trial, 326 youths age 13 to 17 with schizophrenia were randomly assigned to treatment with lurasidone 80 mg, lurasidone 40 mg, or placebo [18]. At treatment end, subjects in both the lurasidone 80 mg and the lurasidone 40 mg demonstrated greater improvement than placebo on the Positive and Negative Syndrome Scale (PANSS), a 210-point scale measuring symptom severity in schizophrenia (least squares [LS] mean change from baseline -18.3; -18.6; -10.5 respectively).

- **For agitation or aggression** – For individuals with agitation or aggression, we typically use olanzapine or risperidone. As an example, in an adolescent with agitation we would typically begin olanzapine at 5 mg orally each day and titrate by 5 mg every five days, if needed, to a maximum of 30 mg per day. If necessary (eg, severe aggression, emergency situation), we use olanzapine intramuscular (IM) formulation, typically beginning at 5 mg IM. We monitor metabolic parameters on a regular basis (table 1).

- **For prominent mood symptoms** – For individuals with prominent symptoms of mood dysregulation or co-occurring depression we prefer to use aripiprazole due to its efficacy

in treating schizophrenia and bipolar disorder in youth and its efficacy in augmenting depression in adults [15,41]. In an adolescent with schizophrenia and prominent depressive symptoms we would begin aripiprazole at 2 mg and titrate by 3 to 5 mg every three days until therapeutic range of 10 to 30 mg is reached. We then monitor for up to one week for response to treatment (table 2). (See "Unipolar depression in adults: Treatment with second-generation antipsychotics", section on 'Aripiprazole'.)

In a clinical trial, 146 patients age 13 to 17 with schizophrenia were randomized to receive either aripiprazole or placebo for a 52-week maintenance period [15]. Over the course of the study, patients assigned to receive aripiprazole experienced a longer mean time to exacerbation of psychotic symptoms/impending relapse compared with placebo (hazard ratio 0.46, 95% CI 0.24-0.88). Aripiprazole had lower rates of treatment-emergent adverse events compared with placebo (3.1 versus 12.5 percent). Rates of weight gain, extrapyramidal symptoms, and somnolence in the aripiprazole group were similar or lower compared with the placebo group.

- **For prominent insomnia** – For individuals with prominent insomnia, we typically use quetiapine, a second-generation antipsychotic with sedating properties. As an example, in an adolescent child with schizophrenia and prominent insomnia, we would begin quetiapine at 25 mg at night and titrate by 25 to 50 mg daily to a total daily dose of 200 mg. Once at 200 mg we would monitor for effect prior to increasing further. (See 'Starting and titrating antipsychotics' below and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Sedation'.)

  In a trial, 220 youths age 13 to 17 with schizophrenia were randomized to treatment with either quetiapine 400 mg, quetiapine 800 mg, or placebo over six weeks [20]. At treatment end, subjects in both the 800 mg and the 400 mg groups demonstrated greater improvement than placebo on the PANSS (LS mean change from baseline 28.4; 27.3; 19.1 respectively).

- For youths with prominent trauma symptoms we typically use risperidone as a first choice. When using risperidone, we would start with 0.5 to 1 mg daily. Depending on symptom severity, tolerance, and response, we increase by 0.5 mg every two to three days for individuals in inpatient treatment, or every one to two weeks in the outpatient setting.

STARTING AND TITRATING ANTIPSYCHOTICS

We start children and adolescents at the low end of the initial dose range and titrate over several weeks (table 2). Due to more rapid metabolism in children and adolescents, we typically give doses at a greater frequency, as compared with adults, over the course of a day. There are no published, widely agreed upon recommendations for antipsychotic doses in youth. The dose of antipsychotics is dependent upon age and past history of treatment with antipsychotics. In individuals with no prior history of treatment with antipsychotics we use the lowest end of the initial starting dose.

For example, in an adolescent with schizophrenia who has never been treated with antipsychotic medication, when treating with risperidone we would start at 0.25 mg per day and increase by 0.25 to 0.5 mg every three to five days in divided doses. Once at the low end of the therapeutic range (eg, 2 mg), we typically monitor for clinical response (eg, decrease in positive symptoms of psychosis, functional improvement as reported from the family or school, or 25 percent decrease in brief psychiatric rating scale).

- In patients with severe symptoms (eg, frequent hallucinations, paranoia), we wait three days for evidence of a clinical response once at the low end of the therapeutic range.
- In patients with less severe symptoms (eg, mild paranoia, occasional hallucinations), we wait as long as two weeks for clinical response. If desired effect is not achieved, we then continue to increase the dose within the therapeutic range.

However, in an adolescent with schizophrenia who has had treatment with antipsychotic medications in the past we would typically begin at 0.25 mg twice daily and increase by 0.5 to 1 mg every three to five days in divided doses. Once at the lower end of the therapeutic range (eg, 4 mg), we monitor, as above, for clinical response.

A table describes the doses we generally use for antipsychotics with established efficacy in youth, including the initial dose, dose increments and therapeutic range, for younger and older children (table 2).

MONITORING

We monitor children and adolescents being treated with antipsychotic medications for changes in symptoms, daily functioning, presence of suicidal or homicidal ideation, and metabolic or other adverse effects of medications such as extrapyramidal symptoms. A table lists our preference for monitoring metabolic side effects during antipsychotic treatment (table 1).

Frequency of visits — We typically see individuals on a weekly to biweekly basis during the first three months of treatment.

Frequency of follow-up depends thereafter depends on the presence of ongoing symptomatology, prior history of recurrence of symptoms, adherence to medications, and the level of support available to the patient. As an example, in an individual with ongoing symptoms of psychosis despite beginning treatment with medications and psychosocial interventions or in those with poor adherence to medication, we would continue to monitor and assess on a weekly to biweekly basis. This contrasts with an individual with a good support system whose symptoms have improved or stabilized who we would see monthly after the first three months.

Monitoring symptoms and adverse medication effects

Psychiatric symptoms — We assess psychiatric symptoms and appropriateness of treatment setting at each visit (see 'Treatment setting' above). We assess for worsening psychosis, mood changes, presence of suicidal or homicidal ideation, and treatment adherence at all visits. (See "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis", section on 'Clinical manifestations'.)

Typically, we interview children under 12 together with a parent/guardian to ensure comfort for the youth and clarification from the parent/guardian about observations in the home and at school. We find it helpful to have a conversation in private with the parent/guardian either prior to the visit or during the visit so that parents/guardians can speak freely about their concerns without the child present. This may avoid the patient worrying about the impact their illness may have on their relationship with their supports. When developmentally appropriate, youth are given the option to also be seen individually for further observations. We interview adolescents and their families separately due to the youth's need for developmentally appropriate autonomy and because of concerns of confidentiality. It is then helpful to bring the adolescent and their family together for a shared discussion.

Abnormal involuntary movements and extrapyramidal symptoms — We monitor all children and adolescents on antipsychotic medication for the presence of extrapyramidal symptoms (eg, akathisia, dystonia, or parkinsonism), and tardive dyskinesia at each visit. Additionally, we complete an Abnormal Involuntary Movement Scale every six months (form 1).

Some abnormalities may be severe, reported by the patient and noted by brief visual inspection. Other symptoms may be mild and identified only by careful examination. We typically ask about motor symptoms including restlessness, pacing, slowness of movements, tremor or gait change. Findings suggest specific extrapyramidal symptoms (see "Schizophrenia in adults:

Maintenance therapy and side effect management", section on 'Movement and motor symptoms' and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Side effect management'):

- Akathisia is suggested by a sensation of restlessness, frequent pacing, or an inability to sit still.
- Parkinsonism is suggested by finding masked facies, bradykinesia, tremor, or rigidity.
- Dystonia is a tonic contraction of a muscle or muscle group that is typically disturbing to the patient and obvious to the examiner.
- Tardive dyskinesia is characterized by the following lip smacking, choreoathetoid movements of the tongue, facial grimacing, choreiform or athetoid movements of the extremities or truncal area, or lateral jaw movements.

Management of extrapyramidal symptoms and tardive dyskinesia is discussed elsewhere. (See "Schizophrenia in adults: Maintenance therapy and side effect management" and "Tardive dyskinesia: Prevention, treatment, and prognosis".)

Metabolic dysregulation — We recommend monitoring fasting glucose or hemoglobin A1c, lipid profile, weight, body mass index at regular intervals during the first year and then annually thereafter. A schedule for routine monitoring for metabolic side effects of antipsychotics is on the associated table (table 1). (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Metabolic dysregulation'.)

Other adverse effects — Other adverse effects include sedation, anticholinergic effects (eg, dry mouth, constipation, urinary hesitancy, blurry vision), and orthostatic changes. We assess for the presence of these by direct questioning during the follow-up visits. Side effects of antipsychotic medications used to treat schizophrenia are found on the table and elsewhere (table 3). (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

SUBSEQUENT TREATMENT

For good response — We continue medication indefinitely at the lowest dose that achieves symptom management in all children/adolescents with schizophrenia. We do this to maintain benefits of medications while reducing the risk of adverse effects.

There are no trials looking at discontinuation of treatment, as there is no cure for schizophrenia and there are no known ways to recover from the neuronal damage associated with schizophrenia. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Full response to pharmacologic therapy' and "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis", section on 'Pathogenesis'.)

Partial response or recurrence of symptoms — Some individuals, despite having symptomatic improvement with antipsychotic treatment at a therapeutic dose range, have persistent residual symptoms (eg, incomplete or partial response). Others have a full response to antipsychotic treatment but have intermittent symptom recurrence. If symptoms are bothersome to the patient or impair functioning, we consider the treatment response to be suboptimal. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Partial response or recurrence of symptoms'.)

Our first step in individuals with incomplete response or intermittent symptom recurrence is to assess medication adherence. Additionally, we ask about family stressors, school stressors, and recent trauma. We do this by directly questioning the individual and their caregiver.

For individuals who experience a suboptimal response after confirmed adherence to a trial of greater than six weeks at maximum dose, our preference is to change antipsychotics. However, data informing the optimal approach are limited [42]. We switch from one antipsychotic to another by gradual taper of the first while simultaneously titrating the second. There are no specific agents that are preferred. As with the initial selection, the choice of medication depends on symptoms present (eg, depression, insomnia, agitation), properties of the particular agent, past history, and patient factors such as concerns of weight gain.

We typically taper by approximately 30 percent per week while titrating the second medication at a similar rate. For example, in an adolescent who has not responded to risperidone 6 mg per day we would consider tapering by 2 mg per week to off while simultaneously starting aripiprazole 2 mg and titrating upward by 5 after one week, then by 5 mg weekly until therapeutic range. This transition can typically be completed over two to three weeks.

We generally do not recommend doses above the therapeutic range. Most studies of antipsychotics dosed above the recommended range have found no clear benefit [43]. If used, trials of higher doses should be limited to three months unless there is clear evidence of benefit. Additionally, we typically do not add an additional second-generation antipsychotic agent in patients who have suboptimal response because little empirical evidence supports this practice [44-47].

Clinical trials provide relatively little guidance for individuals who have had suboptimal responses to two second-generation antipsychotics. Our preference is to add a first-generation antipsychotic such as haloperidol or perphenazine as augmentation. An alternative is to consider a trial of clozapine as monotherapy (table 2).

TREATMENT RESISTANCE

We consider individuals who have chronic symptoms that lead to ongoing impairment, despite two or more prior trials of second-generation antipsychotics and one trial of first-generation antipsychotics to have treatment-resistant schizophrenia and evaluate them for clozapine eligibility.

Childhood-onset schizophrenia and early-onset schizophrenia are often resistant to treatment. The Treatment of Early-Onset Schizophrenia Spectrum Disorders study found that more than half of participants did not respond to antipsychotic medication adequately after eight weeks of treatment, regardless of the specific antipsychotic [48]. (See "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis", section on 'Terminology'.)

Clozapine — We prescribe clozapine for youths that have treatment-resistant schizophrenia. Clinical trials in youth with schizophrenia have shown greater efficacy for clozapine as compared with haloperidol, olanzapine and high-dose olanzapine, in the treatment of resistant schizophrenia [17,49-51].

For example, in a 12-week trial, 39 youths with treatment-resistant schizophrenia were randomly assigned to treatment with clozapine or high-dose olanzapine (ie, up to 30 mg per day) [17]. Individuals treated with clozapine had a higher rate of response (ie, a decrease of 30 percent or more on the Brief Psychiatric Rating Scale) than those treated with high-dose olanzapine (66 versus 33 percent). Some of these trials enrolled children as young as seven [49,50].

- **Adverse effects** – Due to its more severe side effect profile, the use of clozapine is restricted to patients that are treatment resistant.

  In a systematic review of 16 trials using clozapine in youth, neutropenia occurred in up to 15 percent of cases and was usually transient while agranulocytosis was rare (<0.1 percent). Neutropenia has been found to be more frequent in clozapine-treated children and adolescents compared with adults. As an example, in an eight-month study of 172 youth (mean age 18 years), 13 percent developed neutropenia [52]; however, the

cumulative risk of agranulocytosis was only 0.8 percent over the first year of treatment [52]. Some of the risk may be mitigated by concurrent treatment with lithium to raise the white blood cell count [53,54].

Children may be at greater risk for seizure when taking clozapine compared with the adult population. We obtain a baseline electroencephalogram in cases with focal deficits on neurologic examination, evidence of neurodevelopmental delay, or other concern of neurologic abnormalities. A repeat electroencephalogram is indicated during dose titration or treatment if there are behavioral changes that could be consistent with seizure [55].

Comparative studies in youth have shown that clozapine can result in increased tachycardia or mean blood pressure compared with olanzapine [50]. Weight gain with clozapine (0.9 to 9.5 kg in a study of 97 youths) was less than olanzapine (3.8 to 16.2 kg in 353 youths) in a review of randomized, cohort, and pharmacoepidemiologic studies [50,56]. Sedation and hypersalivation have been reported in over 90 percent of individuals treated with clozapine [57]. Other common side effects were enuresis, constipation and weight gain. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Adverse effects'.)

- **Monitoring** – Under the Clozapine Risk Evaluation and Mitigation Strategy program in the United States, the risk of agranulocytosis with clozapine is managed through regular monitoring and registry reporting of neutrophil counts. Clozapine is stopped in cases of moderate and severe neutropenia; the medication can be restarted in some patients [52,54].

  Guidelines for prescribing clozapine, including information about pretreatment assessment, administration, treatment monitoring/reporting, and adverse effects in adults, are reviewed separately. The efficacy and side effects of clozapine in youth are described separately.

PATIENT-SPECIFIC CONSIDERATIONS

Co-occurring substance use disorder — Substance use, such as cannabis use, may be a risk factor for development or exacerbation of psychosis [58]. Epidemiologic studies have estimated that 61 to 88 percent of youth 13 to 18 years of age with a mental disorder have a co-occurring substance use disorder [59,60]. (See "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis", section on 'Co-occurring disorders'.)

Our preference is to provide multimodal, integrated treatment addressing both disorders in children with schizophrenia and co-occurring substance use disorders. Components of the integrated program include treatment of both disorders by the same clinician or team, pharmacotherapy combined with one or more psychosocial interventions and collaborative goal setting [5]. (See "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions" and "Pharmacotherapy for co-occurring schizophrenia and substance use disorder".)

The availability of integrated care varies widely, particularly for children/adolescents. There are no trials of integrated care in children/adolescents with schizophrenia and a substance use disorder; clinical trials comparing integrated and parallel treatment in adults have shown mixed results [6,7]; however, it is supported by a broad consensus among researchers and clinicians with expertise in the area [8,9].

Co-occurring mental disorder — We recommend addressing co-occurring disorders concurrently if the symptoms warrant clinical attention. However, few clinical trials have tested treatments of co-occurring mental disorders in youth with schizophrenia.

Youth with psychotic symptoms or those with clinical high risk for psychosis have increased rates of trauma exposure including physical, emotional, and sexual abuse [61]. Trauma-focused cognitive-behavioral therapy may be helpful for patients diagnosed with schizophrenia that also exhibit symptoms of posttraumatic stress disorder in youth. (See "Depression in schizophrenia" and "Anxiety in schizophrenia" and "Posttraumatic stress disorder in children and adolescents: Trauma-focused psychotherapy", section on 'Individual trauma-focused psychotherapy'.)

Poor adherence — We occasionally use long-acting injectable (LAI) antipsychotics for older adolescents (≥16 years) with poor adherence. In these cases, we typically use them at the same dose as adults.

- **LAI formulations** – Although less commonly used in youth than in adults, LAI antipsychotics are used in patients with schizophrenia who have difficultly adhering to daily oral dosing. There has been little rigorous testing of LAI antipsychotics in this population, though published research supports the safety and efficacy of the formulation:

  - A randomized clinical trial in 113 adolescents (age 12 to 17 years) with schizophrenia randomly assigned to paliperidone extended-release or oral aripiprazole for eight weeks [62]. Both groups improved over the course of the trial; no difference was seen in response rates between the two drugs (67.9 versus 76.3 percent). Risk of

extrapyramidal symptoms was slightly higher in paliperidone extended-release over aripiprazole.

- Open trials and case reports have described the use of LAI antipsychotics in 36 children (mean age of 12 years) with bipolar or schizophrenia spectrum disorders [63]. Twenty-four subjects received LAI risperidone and eight received paliperidone palmitate. Fluphenazine decanoate, aripiprazole extended-release injectable, zuclopenthixol decanoate, and olanzapine extended-release were each used in one patient case reports. Most cases reported clinical improvement and the majority of individuals were reported to tolerate the medication well.

Optimal dosing of LAI antipsychotics for pediatric schizophrenia is not known. In our clinical experience, older adolescents (≥16 years) are treated with LAI antipsychotics using adult dosing with results similar to those seen in adults (table 4).

Treatment of schizophrenia in adults with LAI antipsychotics is reviewed separately. (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

First-episode psychosis — Emerging data suggest that first-episode psychosis treatment programs are associated with improved clinical outcomes compared with treatment as usual [64-66]. The programs typically include intensive case management, psychiatric medication management, and psychological and peer support. Many of these programs do not include patients under the age of 18. Treatment of first-episode psychosis is reviewed separately. (See "First episode psychosis".)

CLINICAL HIGH RISK FOR PSYCHOSIS SYNDROME

Attenuated psychosis syndrome is a proposed syndrome of psychoses that is less severe, more transient, and with relatively preserved insight. Individuals with attenuated psychosis syndrome are at increased risk for psychotic disorder [67].

The criteria for these high-risk states vary, ranging from prodromal symptoms (ie, disorganized or unusual thought content such as paranoia or suspiciousness, disorganized behavior) to the presence of psychotic symptoms below the threshold of a psychotic disorder.

Despite limited evidence we begin treatment to lessen the risks of conversion to psychosis and the associated developmental and learning impairments [68]. We begin treatment with the following treatments.

- **Selective serotonin reuptake inhibitors (SSRIs)** – We typically begin treatment of depressed and anxious children and adolescents with clinical high risk for psychosis with an antidepressant. In many cases, the presence of co-occurring disorders may warrant treatment with an SSRI. However, we are cautious in beginning antidepressants as a psychotic presentation in childhood could be due to a bipolar diathesis and use of an antidepressant may precipitate further mood symptoms. We screen for mania and family history of bipolar illness prior to starting an SSRI.

  As an example, in an adolescent with prodromal symptoms that include severe anxiety or the presence of an anxiety disorder, treatment with fluoxetine starting at 10 mg per day up to a maximum of 40 mg per day may help lessen symptoms of anxiety as well as lessen the risk of conversion to psychotic disorder.

  Data from prospective studies appear to show that treatment of individuals with clinical high risk of psychosis with an antidepressant is associated with a decreased rate of conversion to a psychotic disorder as compared with antipsychotic medications [69-71]. For example, in a prospective study including 152 adolescents with prodromal symptoms, 20 subjects were treated with an SSRI and 28 were treated with second-generation antipsychotic medication [69]. While all individuals that converted to a psychotic disorder had been treated with antipsychotic medications rather than antidepressants, outcomes were confounded by greater nonadherence to antipsychotic medications than antidepressant medications (61 versus 20 percent).

- **Psychosocial interventions** – We offer cognitive-behavioral therapy (CBT), cognitive enhancement therapy, and age-appropriate educational/vocation skills training and support for children and adolescents with prodromal symptoms.

  While clinical trials support their efficacy for treatment of schizophrenia in adults, few trials have tested their efficacy for youths with schizophrenia or in preventing or slowing functional deterioration in youths with prodromal symptoms.

  In a clinical trial, 51 youths/young adults (age range 14 to 30) at “ultra-high” risk for psychosis were randomly assigned to six months of treatment with either CBT or supportive therapy [72]. At 6- or 12-month follow-up, similar improvements were found between groups in attenuated positive symptoms, anxiety, and depression. These findings are consistent with our clinical experience in suggesting that all youth with high-risk symptoms would benefit from supportive or CBT as well as close clinical monitoring for conversion to psychosis.

- **Omega-3 fatty acids** – We typically suggest treatment with long-chain omega-3 polyunsaturated fatty acids (PUFAs; 500 to 1000 mg twice daily) to children or adolescents with subthreshold psychotic symptoms.

  Clinical trials show mixed efficacy for long-chain omega-3 polyunsaturated fatty acids on the rate of transition to a psychotic disorder among these individuals [73,74]. For example, in one trial, 81 youths age 13 to 25 with prodromal psychosis were randomly assigned to receive omega-3 PUFAs (1.2 grams/d) or placebo for 12 weeks [73]. At 12-month follow-up, a lower percentage of those treated with omega-3 PUFAs compared with those treated with placebo, had transitioned to a psychotic disorder (5 versus 28 percent). Adverse effects did not differ between groups. However, in another trial including 304 youths with high risk for psychosis randomly treated with omega-3 PUFAs or placebo, rates of transition to psychosis after six months was similar [74]. The general health benefits of PUFAs and the lack of clinically relevant adverse effects support its use among children and adolescents with subthreshold psychotic symptoms. Further trials are needed to confirm efficacy of this treatment.

The use of antipsychotic medication in prodromal or high risk of psychosis individuals with the aim of delaying or preventing conversion to psychosis is controversial and not supported by clinical trials [75,76].

Repeated or prolonged psychotic episodes have deleterious neuropsychological, neurophysiological, and brain structural effects on patients who have been diagnosed with a first psychosis [5-9]. Additionally, evidence suggests that prolonged periods of untreated psychosis may result in increased resistance to conventional treatments [10,11].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

SUMMARY AND RECOMMENDATIONS

- **Initial treatment** – Our first-line treatment for children and adolescents with schizophrenia is with a combination of pharmacologic management and adjunctive psychosocial intervention. (See 'Antipsychotic medications' above.)

- **Pharmacologic management** – Antipsychotic medication is the cornerstone of treatment of youths with schizophrenia (table 2).

  - **Selection of antipsychotic** – For most children and adolescents with schizophrenia, we suggest using a second-generation antipsychotic rather than a first-generation antipsychotic (**Grade 2C**). Our preference is based on their lower rates of extrapyramidal symptoms and tardive dyskinesia compared with first-generation antipsychotics. (See 'Choosing an antipsychotic medication' above.)

    We base our choice of the specific second-generation agent by the clinical features of the individual (eg, agitation, mood symptoms, weight sensitivity), properties of the antipsychotic, and past response to the agent.

  - **Pharmacotherapy in youths** – Children and adolescents, compared with adults, are at higher risk of many of the side effects associated with antipsychotic use, including extrapyramidal symptoms, withdrawal dyskinesias, elevated prolactin, weight gain, and metabolic abnormalities. Tardive dyskinesias are less common in youth compared with adult and older adult populations. (See 'Pharmacotherapy in youths' above.)

- **Adjunctive psychosocial treatment** – We suggest adjunctive psychosocial treatment, rather than pharmacologic monotherapy for all children and adolescents with schizophrenia (**Grade 2C**). Appropriate interventions include psychoeducation, cognitive-behavioral therapy, cognitive enhancement, and age-appropriate vocational skills training. (See 'Psychosocial treatment' above.)

- **Monitoring** – We monitor all children or adolescents in the least restrictive environment where the safety of the individual can be maintained.

  We typically see individuals in weekly or biweekly follow up during the first three months of treatment. Further frequency depends on response to treatment. (See 'Monitoring' above.)

  We monitor psychiatric symptoms including psychosis, mood changes, suicidal and homicidal ideation, and treatment adherence at each visit. (See 'Psychiatric symptoms' above.)

  We monitor for the presence of extrapyramidal symptoms and tardive dyskinesia at each visit. We complete an Abnormal Involuntary Movement Scale every six months (form 1). (See 'Abnormal involuntary movements and extrapyramidal symptoms' above.)

We monitor for metabolic dysregulation at regular intervals (table 1). (See 'Monitoring symptoms and adverse medication effects' above.)

- **Subsequent treatment**

  - **For good response to treatment** – We continue medication indefinitely and at the lowest possible dose that achieves symptom management in all children/adolescents with schizophrenia. (See 'For good response' above.)

  - **Partial response or recurrence** –For individuals who experience a partial response after confirmed adherence to a trial of greater than six weeks at maximum dose, our preference is to change antipsychotics. For individuals who have had suboptimal responses to two second-generation antipsychotics data informing the optimal approach are limited. Our preference is to add a first-generation antipsychotic such as haloperidol or perphenazine as augmentation. An alternative is to consider a trial of clozapine as monotherapy. (See 'Partial response or recurrence of symptoms' above.)

- **Treatment resistance** – Youth with schizophrenia who have an inadequate response to two or more adequate trials of second-generation antipsychotics and one trial of a first-generation antipsychotic are considered to have treatment resistance.

  We suggest treatment with clozapine rather than treatment with another antipsychotic for all children and adolescents with treatment resistant schizophrenia (**Grade 2B**). (See 'Treatment resistance' above.)

- **Co-occurring substance use disorder or other mental disorder** – We address both disorders simultaneously using multimodal treatment including pharmacologic and psychosocial interventions.

- **Clinical high risk of psychosis** – For youth with a clinical high risk of psychosis (ie, disorganized or unusual thought content such as paranoia or suspiciousness, disorganized behavior), we suggest treatment with a selective serotonin reuptake inhibitor such as fluoxetine rather than an antipsychotic medication (**Grade 2C**). Additionally, we treat these patients with omega-3 fatty acids and psychosocial interventions to the extent that they are available. (See 'Clinical high risk for psychosis syndrome' above.)

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