

Clinical Practice Guidelines for the Management of Schizophrenia in Children and Adolescents

Sandeep Grover, Ajit Avasthi

Department of Psychiatry, PGIMER, Chandigarh, India

INTRODUCTION

Schizophrenia is understood as a chronic disabling condition, which has a significant negative impact on the life of a patient and their family. When the onset of illness for schizophrenia is before 18 years of age, it is known as early-onset schizophrenia (EOS). Further, based on the age of onset, schizophrenia is categorized as very early onset schizophrenia (VEOS) when the age of onset is <13 years and EOS when the age of onset is between 13 and 18 years. When the onset of illness is before 13 years of age, it is known as childhood-onset schizophrenia (COS). Epidemiological data suggest that onset of schizophrenia in childhood is rare, especially before the age of 6 years. The peak age for onset of schizophrenia is considered to be 15–30 years. The prevalence of various psychotic disorders has been reported to be 0.4% among children and adolescents aged 5–18 years. In terms of relationship between age of onset and gender, it is suggested that EOS is more often seen in males; however, there is equal distribution between both the genders, as the age of onset increases.

SCOPE OF THE DOCUMENT

These guidelines are based on the recent developments in the area of management of EOS. These guidelines are not designed specifically for any treatment setting, and minor modifications may be required based on the needs of the patients in a specific setting. These guidelines are not a substitute of professional knowledge of a treating psychiatrist; instead, these guidelines provide a broad framework for the assessment and management of patients

with EOS, and these may have to be tailored to the needs of the individual patient.

ASSESSMENT

A thorough assessment of a patient and their family members/caregivers need to be done. The most important aspect of assessment is obtaining a detailed history from all possible sources and carrying out a thorough physical examination and mental state examination [Table 1]. Diagnosis of schizophrenia in children and adolescent is also established using the same criteria of International Classification of Diseases and Diagnostic and Statistical Manual as used for adults. In general, it is said that validity of diagnosis of schizophrenia in children <6 years has not been established. Patients with COS are often misdiagnosed, especially during the time of onset of illness. The common misdiagnosis includes developmental disorders, obsessive-compulsive disorder, affective disorders, and other psychotic disorders. Proper diagnosis requires detailed history-taking with focus on the evolution of the illness and proper mental status examination. Many a times, diagnosis is not clear at the first instance and proper establishment of diagnosis may require multiple assessments including repeated mental status examination.

The assessment should cover evaluation of various symptom dimensions, severity of symptoms, comorbid psychiatric and medical conditions, particularly comorbid substance abuse, risk of harm to self or others, level of functioning, and socio-cultural milieu of the patient. Onset of EOS is usually insidious. Patients with EOS may have a history of social withdrawal and isolation, academic difficulties, behavioral problems, speech and language difficulties, and

Address for correspondence: Prof. Sandeep Grover,
Department of Psychiatry, PGIMER, Chandigarh, India.
E-mail: drsandeepg2002@yahoo.com

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cognitive problems. In general, patients with EOS exhibit features of hallucinations, thought disturbance, and flat affect. Delusions and catatonic symptoms are less frequently encountered compared to hallucinations. However, while evaluating children and adolescents, it is important to distinguish psychopathology from normal childhood experiences such as imagination and fantasy. Similarly, before labeling something as formal thought disorder, it is important to consider the speech and language difficulties associated with developmental disorders. It is important to remember that all children who report hallucinations do not necessarily have schizophrenia or other psychotic disorders. Children with autism spectrum disorders can have fantasies and odd beliefs (able to talk to inanimate toys), social awkwardness, and concrete thinking. If the clinicians are not very well versed with the presence of these features in children with autism spectrum disorder and fail to take a developmental perspective, many a times these children are diagnosed with EOS. In general, when the child presents with odd behavior from very early age along with deficits in social and communication domains, in the absence of clear-cut psychotic symptoms, it is important to first consider the possibility of autism spectrum disorder, rather than EOS. However, it is important to remember that many children and adolescents with autism spectrum disorder go on to develop schizophrenia later on.

Sometimes, children and adolescents with schizophrenia may present with symptoms of odd behavior and social withdrawal symptoms. Such children should be evaluated for personality disorders such as schizoid and schizotypal disorder before considering the diagnosis of schizophrenia. Usually, compared to adolescents with schizophrenia, adolescents with schizoid and schizotypal disorders may have persistent pattern of thinking, emotional coldness, and odd behaviors. Usually, evaluation of history of the patients with personality disorders will reveal the presence of stable and pervasive patterns of thinking, which is significantly in odds with the sociocultural norms; in contrast, in patients with schizophrenia, there may be evidence of otherwise normal personality, before the emergence of symptoms of schizophrenia. When the diagnosis is not clear, it is advisable to keep the diagnosis open and follow-up of the patient over time, which helps in clarification of the diagnosis. Many patients with schizoid and schizotypal disorder also go on to develop schizophrenia later on.

Whenever feasible and when diagnosis is in doubt, it is suggested that clinician can utilize semi-structured interviews such as schedule for affective disorders and schizophrenia for school-age children aged 12 years or the Kiddie Schedule for Affective Disorders and Schizophrenia. Further, wherever feasible, unstructured assessments can be supplemented using appropriate standardized rating scales.

Many patients with EOS will also have cognitive disturbances in the domains of memory, attention, and executive function

Table 1: Assessment of patient presenting with early-onset schizophrenia

- Basic assessments
 - Comprehensive assessment of patients and family members
 - Obtain history with information from all possible sources, while taking history focus on the features present before outbreak of psychotic symptoms
 - Take a developmental perspective while history taking
 - Obtain history to rule out other possible causes of psychotic features
 - Substance use history
 - Educational history: performance, recent decline, educational attainment, peer relationships, school-related issues
 - Carry out a thorough physical examination to rule out possible medical causes, evaluate for soft neurological signs, minor congenital anomalies
 - Record baseline blood pressure, weight, body mass index and wherever indicated waist circumference
 - Detailed mental state examination
 - Consider the possible differential diagnosis by ruling out secondary psychoses and other psychiatric disorders
 - Establish diagnosis according to current diagnostic criteria
 - Evaluate for possible comorbidities: attention deficit hyperkinetic disorder, oppositional defiant disorder, affective disorders (depression/mania), separation anxiety disorders, other anxiety disorders, OCD, tics
- Psychosocial assessment: social support, social networks, family environment, coping of patient and family members, stigma experienced/perceived by the patient and the family members, psychological distress among the caregivers
- Areas to be evaluated: severity of symptom, various symptom dimensions (reality distortion, disorganization, negative, depressive and cognitive symptoms), comorbid physical, psychiatric and substance use conditions, risk of harm to self and others, level of functioning and socio-cultural milieu of the patient
- Basic investigations: hemogram, blood glucose and lipid levels, liver function test, renal function test, serum calcium, electrocardiogram (focus on QTc), thyroid function test, neuroimaging (magnetic resonance imaging), electroencephalogram, metabolic profile
- Optional Investigations: Vitamin D levels, Vitamin B 12 levels, urinary porphobilinogen, serum ceruloplasmin levels, serum prolactin levels
- Assessments of caregivers: knowledge and understanding of the illness, attitudes, and beliefs regarding treatment, impact of the illness on them, personal and social resources
- Ongoing assessments: response to treatment, side effects, treatment adherence, the impact of patient's immediate environment, disability assessments, other health-care needs, ease of access and relationship with the treatment team
- Additional/optional assessments
 - Use of standardized rating scales to rate all aspects of the illness
 - Psychological assessments, if required: tests for intelligence quotient, detailed cognitive assessment

OCD – Obsessive-compulsive disorder

and in the form of overall global impairment. Looking at the old records or proper history-taking often reveals preexisting cognitive disturbance in the in the domains of attention, processing speed, verbal reasoning, and working memory. Some of these problems may manifest as academic decline or problems in academics. While evaluating the functional decline, it is important to evaluate at the decline in or failure to achieve age-appropriate interpersonal skills and academic achievements. Besides mental status examination, it is important to carry out a thorough physical examination to rule out medical causes of psychotic symptoms and to evaluate for comorbid physical illnesses.

Rule out possible medical disorders and other psychiatric disorders: Before considering the diagnosis of schizophrenia, it is important to rule out other psychiatric disorders and underlying medical illnesses, which can have similar manifestations [Table 2]. Ruling out underlying medical illnesses is of paramount importance in children and adolescents because psychosis in children has been reported to be associated with inborn errors of metabolism, various genetic syndromes (such as Juvenile Huntington's disease, Klinefelter syndrome, Turner syndrome, and Prader-Willi/Angelman syndrome), autoimmune disorders, endocrine diseases, nutritional deficiencies, and central nervous system infections. Features which should alert a clinician for possible organic cause include acute/abrupt onset of illness, onset of illness in the background of recent surgery, viral infection or medications, cognitive or developmental regression, and presence of atypical features such as visual hallucinations and lack of negative symptoms. Other clinical features which prompt for evaluation of organic causes include presence of confusion, catatonia, development of rare or serious neurological side effects, presence of seizures, presence of ataxia, neuropathy, stroke, skin lesions, cataract, malar rash, hepatosplenomegaly, gastrointestinal signs, and dysmorphic facial appearance. Inborn errors of metabolism should be suspected, while the early development history suggests the presence of severe hypotonia during the initial part of life, developmental delay, presence of dysmorphic features, history of nausea, diarrhea and other gastrointestinal features, presence of catatonia, and cognitive decline.

Certain clinical conditions such as mood disorders, substance-induced psychoses, and psychoses secondary to physical illnesses may present with similar picture as EOS. These conditions must be ruled out on the basis of detailed history, examination, and additional investigations. Detection of comorbid substance abuse/dependence requires high index of suspicion, and wherever facilities are available, urine or blood screens (with prior consent) can be used to confirm the presence of comorbid substance abuse/dependence. Detailed physical examination needs to be done to rule out the presence of any physical illness and also to rule out psychoses secondary to physical illnesses. A study reported that possibility of an underlying organic cause need to be suspected if the history is characterized by atypical description (such as very early onset of symptoms, acute onset, onset of illness apparently triggered by surgery, viral infections or use of medications, cognitive regression, and behavioural regression), atypical clinical features (such as confusion, catatonia, evidence of rare or serious neurological adverse reaction to treatment), and presence/possibility of physical symptoms (such as seizures, presence of malar rash, gastrointestinal signs, and dysmorphic features).

Investigations: Investigations must be carried out judiciously. However, if physical illnesses are suspected,

then the clinicians should not hesitate to carry out specific investigations to rule out the same. Basic laboratory investigations include hemogram, liver function tests, renal function test, and electrocardiogram. If the substance use is suspected, then urine tests for substances of abuse may be done. Other investigations may also be done based on the history and finding of the physical examination. Wherever feasible, cognitive assessment needs to be done. Neuroimaging can be done when neurological illnesses are suspected. It is important to take sexual history in young patients and document the last menstrual period in those adolescents who are sexually active and urine pregnancy test may be considered in these patients before starting antipsychotic medications. *Assessment of family/caregivers:* Assessment of parents/family members must involve assessment of their knowledge and understanding about the disorder, their attitudes and beliefs with respect to the treatment, impact of the illness on them, and their personal and social resources.

Making the diagnosis: At times, a definitive diagnosis of EOS requires time and repeated assessments. In fact, it is suggested that diagnosis of schizophrenia must be made with great caution and sensitivity as it is associated with significant negative psychosocial consequences, both for the patient and also for their caregivers. Whenever the diagnosis is in doubt, it is better to observe the patient without prescribing any antipsychotic medications. However, decision to keep the patient off medication must be evaluated against the risks of delaying treatment or the potential for harm to self and others in acutely ill patients. As in other age groups, the diagnosis of schizophrenia is not a one-time affair, but a continuous process and based on the subsequent information from patients and caregivers, and on repeated clinical evaluations, the diagnosis may need re-evaluation.

At-risk mental state (ARMS): At times, patients are brought to the clinic in whom the diagnosis of schizophrenia cannot be made with certainty; however, in view of symptom profile, these patients are considered as having prodrome of schizophrenia or "at-risk mental state (ARMS)" subject. The symptoms in these subjects may be in the form of disturbances in emotion, cognition, perception, communication, motivation, and sleep. These features are labeled differently by various diagnostic symptoms such as basic symptoms, attenuated positive symptoms, brief limited intermittent psychotic symptoms, features of schizotypal personality disorder, and genetic risk paired with functional deterioration. Other commonly used term for this group of patients is "ARMS." People with ARMS may manifest with symptoms of low mood, anxiety, social isolation, educational/occupational failure, and brief/intermittent psychotic symptoms, which are also known as attenuated psychotic symptoms. The duration of prodrome can vary from patient to patient,

Table 2: Differential diagnosis of schizophrenia in children and adolescents

Other psychiatric disorders Other psychotic disorders: acute and transient psychosis, delusional disorder Schizoaffective disorder Severe depression with psychotic symptoms Bipolar disorder (mania/depression with psychotic symptoms) OCD Posttraumatic stress disorder Autism/autism spectrum disorder Personality disorders: schizoid, schizotypal Childhood disintegrative disorders	Neurological disorders Parkinson disease Wilson disease Huntington disease Sydenham chorea Idiopathic basal ganglia calcification Spinocerebellar degeneration Myelin diseases Adrenoleukodystrophy Marchiafava-Bignami disease Multiple sclerosis Seizure (especially complex partial seizures) Hydrocephalus Hypoxic encephalopathy Narcolepsy Cerebrovascular accident Trauma (especially to frontal and temporal regions)
Substance-induced disorders Cannabis Dextromethorphan Lysergic acid diethylamide Hallucinogenic mushrooms Psilocybin Peyote Cannabis Stimulants Inhalants Alcohol Phencyclidine Prescription drugs (including steroids, corticosteroids, anesthetics, anticholinergics, antihistamines, and amphetamines) Withdrawal from alcohol, hallucinogens, opiates, psychostimulants, or sedative-hypnotics	Autoimmune disorders Systemic lupus erythematosus Temporal arteritis Anti-NMDA receptor encephalitis EAATDs
Poisoning Anticholinergics Carbon monoxide Heavy metals	Infections Herpes simplex HIV Syphilis Parasitic infections Toxoplasmosis Viral encephalitis Lyme disease
Endocrine disorders Addison's disease Cushing disease Hypothyroidism/hyperthyroidism Hyperparathyroidism Panhypopituitarism	Metabolic disorders Porphyria Hyperhomocysteinemia Metachromatic leukodystrophy
Nutritional deficiencies Thiamine deficiency Folate deficiency B12 deficiency Pellagra (niacin deficiency)	Miscellaneous conditions Neoplasm Inborn errors of metabolism

NMDA – N-methyl-D-aspartate; EAATDs – Encephalopathy associated with autoimmune thyroid diseases; OCD – Obsessive-compulsive disorder

from few weeks, months, to years. In patients who present with vague symptoms and in whom prodrome is suspected, it is important to use specific assessment instruments to evaluate the prodrome or the ARMS. Some of the instruments which can be used for assessment of these patients include instrument for the retrospective assessment of onset of schizophrenia, scale for prodromal symptoms, structured interview of prodromal symptoms, and comprehensive assessment of ARMS. However, it is

important to remember that all patients with prodrome do not go on to develop psychotic disorders. However, it is important to closely follow-up these patients for emergence of psychosis. Psychological intervention can be provided to these patients.

Over the period of treatment, the focus of assessment should shift to assessment of response to treatment, side effects experienced by the patient, monitoring of metabolic

side effects, medication adherence, treatment adherence, educational difficulties, evaluation of disability, other health care needs, and impact of the illness on the patient and caregivers.

FORMULATING A TREATMENT PLAN

As with adult patients with schizophrenia, formulation of treatment plan involves deciding about treatment setting, treatments to be used, and areas to be addressed [Figure 1]. Treatment plan should be drawn by consulting all the persons involved in the care of the patient. The treatment plan formulated should be feasible, flexible, and practical to address the needs of the patients and the family members. The treatment plan should be continuously modified based on the regular assessment of the patient and the family members.

CHOICE OF TREATMENT SETTING

Patients with EOS must be managed in the least restrictive environment. Most of the patients can be managed on outpatient basis. However, some of the patients may require inpatient care. The indications for inpatient care are given in Table 3. All the patients admitted to the inpatient setting should have accompanying family caregivers. Whenever inpatient care facilities are not available, then the family needs to be informed about the need for inpatient care and admission in the nearest available inpatient facility may be facilitated. However, it is to be remembered that rules as laid by the Mental Health Care Act, 2017, need to be abided in providing inpatient care to children and adolescents.

TREATMENT OPTIONS FOR THE MANAGEMENT OF EARLY-ONSET SCHIZOPHRENIA

Treatment options for the management of schizophrenia include antipsychotic medications, psychoeducation, psychosocial interventions, adjunctive medications, and electroconvulsive therapy (ECT) [Table 4].

Antipsychotics

Antipsychotic medications are considered as the first-line treatment for patients with EOS. However, these are recommended to be used along with psychosocial interventions. Compared to data in adults, the efficacy data on use of antipsychotic medications in children and adolescents are limited. Further, all the antipsychotics have not been evaluated in patients with EOS aged <18 years. Most of the antipsychotics have been evaluated in patients aged 13–18 years. The antipsychotics which have been evaluated in one or more randomized controlled trial (RCT) include haloperidol, aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, ziprasidone, and clozapine. Majority of the studies which have evaluated different antipsychotics in adolescent patients have been

industry-sponsored. One of the non-industry-sponsored studies which have evaluated the efficacy of different antipsychotics in patients with schizophrenia/schizophrenia spectrum disorder includes Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) study. Many meta-analyses have evaluated the existing short-term (6–12-week trials) efficacy/effectiveness data with respect to use of antipsychotics in children and adolescents with schizophrenia [Table 5]. Some of the common conclusions of these meta-analyses include superior efficacy of antipsychotic medications when compared to placebo (except possibly for ziprasidone), lack of significant difference in efficacy between First generation Antipsychotic Medications (FGAMs) and Second Generation Antipsychotic Medications, and tolerability of SGAMs being better than FGAMs. Overall, antipsychotics have superior efficacy in terms of reduction in positive symptoms, and there is lack of significant beneficial effect on negative symptoms when compared to placebo. Data also suggest that there is no difference in efficacy between different SGAMs, except for the fact that clozapine is superior to other antipsychotics. SGAMs

Table 3: Indications for admission in patients with early-onset schizophrenia

- Those who express suicidal ideas of a definite sort, or who have made an attempt of suicide
- Those who harm themselves, or threaten to harm others
- Presence of severe agitation or violence which puts the life of others at risk
- Those who require prolonged observation for clarification of diagnosis
- Refusal to eat which puts the life of patient at risk
- Severe malnutrition
- Patient unable to care for self to the extent that she/he requires constant supervision or support
- Catatonia
- Presence of general medical or comorbid psychiatric conditions which make management unsafe and ineffective in the outpatient setting
- Subjects who have problems with treatment compliance or delivery, leading to unduly protracted treatment
- Those who require ECT
- Those who require removal from a hostile social environment
- Admission required for observation to clarify the diagnosis

ECT – Electroconvulsive therapy

Table 4: Options for management for schizophrenia

- Antipsychotic medications
 - FGAMs
 - SGAMs
- Psychosocial interventions
 - Family intervention, cognitive behavioral therapy, social skills training, cognitive remediation, individual therapy, group therapy, vocational rehabilitation, early-intervention programs, case management, community mental health teams, crisis resolution teams
- Adjunctive medications
 - Anticholinergics, antidepressants, benzodiazepines, hypnoticsedatives, anticonvulsants, lithium carbonate
- Somatic treatments
 - ECT
- Other measures
 - Lifestyle and dietary modifications

FGAMs – First-generation antipsychotic medications;

SGAMs – Second-generation antipsychotic medications;

ECT – Electroconvulsive therapy

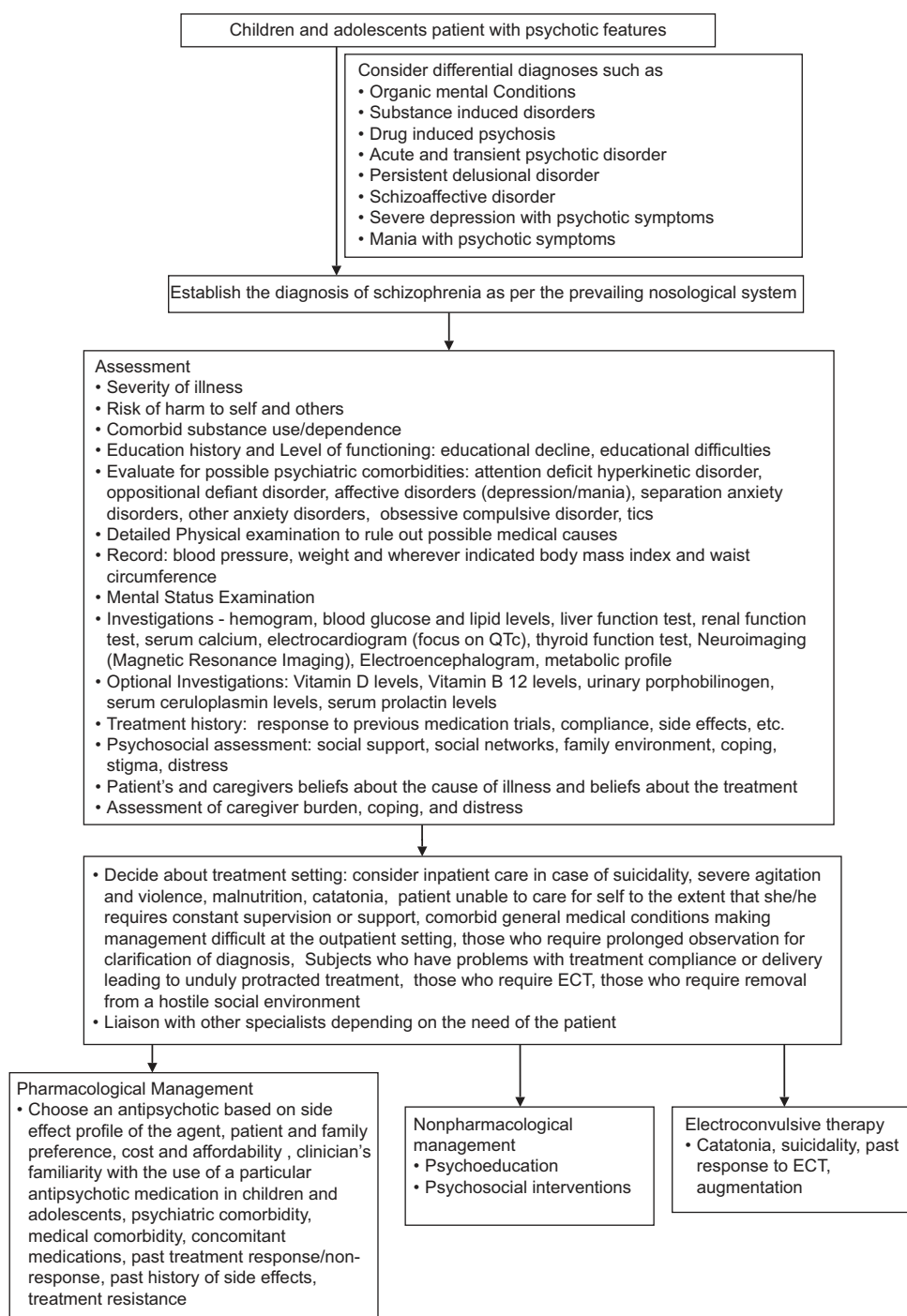


Figure 1: Initial evaluation and management plan for schizophrenia in children and adolescents

are associated with lower dropout rates compared to FGAMs. In terms of adverse effects, there is differential adverse effect profile of various antipsychotics, with extrapyramidal symptoms being more common in patients receiving FGAMs, hyperprolactinemia being more common with risperidone and FGAMs, and weight gain and metabolic side effects being more common with SGAMs, especially olanzapine. It is in general also suggested that side effect of antipsychotics in adolescents is similar to that seen in adult patient, except for the fact that adolescents experience more side effects.

Little is known about the predictors of response to treatment in patients with EOS. In TEOSS study, which was a National Institute of Health sponsored study, which compared response to olanzapine, risperidone, and molindone. This study evaluated the predictors of response and reported that higher severity of symptoms at the baseline, history of being in an early education program and previous prescription of a mood stabilizer were associated with better treatment response. Higher dropout rates were associated with aggressive behaviors as

per the report of the parents and being of African-American origin (Gabriel *et al.*, 2017).

There are limited data in terms of long-term efficacy/effectiveness of various antipsychotics in patients with EOS. Patients, who participated in the 8-week DBRCTs as part of TEOSS study, were continued on the same medication in the double-blind fashion for another 44 weeks. This study showed lack of difference in the discontinuation rates between the three antipsychotics used. Only 12% of the patients continued on the originally randomized antipsychotic medication. There was no difference in the efficacy of three antipsychotics used. Molindone was more commonly associated with akathisia, whereas risperidone was more often associated with rise in serum prolactin levels. Although olanzapine and risperidone were

associated with weight gain and metabolic side effects in the acute phase, at the end of maintenance phase, there was no difference between the three antipsychotics.^[8] A survey of Medicaid claims data which evaluated the data related to use of olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone suggests that three-fourth of the adolescents with schizophrenia and related disorders discontinue their medications within 180 days of starting of these antipsychotics, with no significant difference between the various antipsychotic medications.^[9] A naturalistic study evaluated the 6-month outcome of children and adolescent (9–17 years), diagnosed with schizophrenia and other related psychotic disorders treated with olanzapine, risperidone, and quetiapine. In general, there was no significant difference in the effectiveness of these antipsychotic medications. Olanzapine was associated

Table 5: Systematic reviews and meta-analyses evaluating various antipsychotic medications among patients with early-onset schizophrenia

Author	Studies included	Findings
Kumra <i>et al.</i> , 2008 ^[1]	10 DBRCTs evaluating efficacy of antipsychotics in patients with EOS spectrum disorder	Antipsychotic medications better than placebo Clozapine better than haloperidol, standard-dose olanzapine, and high-dose olanzapine Adolescent patients are more sensitive to develop extrapyramidal side effects, weight gain, sedation, hyperprolactinemia SGAMs associated with increased risk of developing diabetes mellitus
Fraguas <i>et al.</i> , 2011 ^[2]	34 studies (9 studies conducted in patients with schizophrenia, 6 included patients with bipolar disorder, and 19 studies included patients with more than one diagnosis)	Clozapine is superior to other antipsychotics in patients with treatment-refractory schizophrenia No significant difference between other SGAMs in terms of efficacy Olanzapine associated with higher weight gain, followed by clozapine, risperidone, quetiapine, and aripiprazole Maximum rise in prolactin levels seen with risperidone, whereas aripiprazole was associated with reduction in prolactin levels; clozapine and quetiapine were prolactin neutral Compared to FGAMs, SGAMs are associated with lower rates of extrapyramidal symptoms This meta-analysis concluded that both FGAMs and SGAMs are better than placebo SGAMs better than the FGAMs in terms of efficacy/effectiveness Clozapine superior to other antipsychotics
Sarkar and Grover, 2013 ^[3]	50 studies included in the meta-analysis, 15 were RCTs	FGAMs are as effective as SGAMs, but SGAMs are better tolerated than FGAMs in short-term SGAMs associated with lesser drop-out rates SGAMs such as olanzapine, risperidone, and clozapine are associated with weight gain No significant difference was seen between various SGAMs in terms of efficacy Standard doses of risperidone were more efficacious than low doses, but same was not true for ziprasidone and aripiprazole
Datta <i>et al.</i> , 2014; ^[4] Kumar <i>et al.</i> , 2013 ^[5]	13 RCTs evaluating the efficacy of antipsychotics among adolescents (age 13-18 years)	SGAMs better than the FGAMs in terms of efficacy/effectiveness Clozapine superior to other antipsychotics FGAMs are as effective as SGAMs, but SGAMs are better tolerated than FGAMs in short-term SGAMs associated with lesser drop-out rates SGAMs such as olanzapine, risperidone, and clozapine are associated with weight gain No significant difference was seen between various SGAMs in terms of efficacy Standard doses of risperidone were more efficacious than low doses, but same was not true for ziprasidone and aripiprazole
Harvey <i>et al.</i> , 2016 ^[6]	11 controlled trials (7 DBRCTs, 3 RCTs, and 1 controlled trial) comprising of 8 different antipsychotics (age <18 years), evaluated in patients with schizophrenia, schizoaffective disorder or schizophreniform disorder, reported outcome in the form of reduction in PANSS	All antipsychotics are superior to placebo, but only 3 antipsychotics, i.e., olanzapine, risperidone, and molindone associated with statistically significant reduction in total PANSS scores at 6 weeks Significant reduction in PANSS positive subscale scores with haloperidol, risperidone, and olanzapine None of the antipsychotics significantly better than placebo in reduction of PANSS negative subscale score
Pagsberg <i>et al.</i> , 2017 ^[7]	12 trials (8-19 years old) involving 8 antipsychotics included in the network meta-analysis, reported outcome in the form of reduction in PANSS	All antipsychotics are superior to placebo (low- to high-quality evidence), except ziprasidone and asenapine (low- to moderate-quality evidence) PANSS total symptom change was comparable among antipsychotics (low- to moderate-quality evidence), except ziprasidone (very low- to low-quality evidence) Side effects Weight gain: primarily associated with olanzapine Extrapyramidal symptoms and akathisia were associated with molindone Rise in prolactin levels associated with risperidone, paliperidone, and olanzapine No difference between various antipsychotics in terms of serious adverse events, discontinuation rates, sedation, insomnia, rise in levels of triglycerides

RCTs – Randomized controlled trials; DBRCTs – Double-blind RCTs; PANSS – Positive and Negative Syndrome Scale; SGAMs – Second-generation antipsychotic medications; FGAMs – First-generation antipsychotic medications; EOS – Early-onset schizophrenia

with significantly higher weight gain when compared with risperidone and quetiapine. However, compared to olanzapine, use of risperidone was associated with more extrapyramidal side effects (EPS).^[10] Long-term data of patient receiving clozapine suggest that among patients with EOS, a very high proportion of patients (72.5%), who are started on clozapine, are maintained on the same for long run (>2 years), rates even exceeding than those reported in patients with adult-onset schizophrenia.

It is to be remembered that depot antipsychotic medications have not been evaluated in children and adolescents.

Choice of antipsychotic medication in children and adolescents

Based on the available evidence, antipsychotic medications are considered as the first-line treatment for schizophrenia in adolescents, which must be used along with the psychosocial management. Among the various antipsychotics, it is generally suggested that SGAMs, other than clozapine, may be used as the first-line agents. The United States Food and Drug Administration have approved haloperidol, molindone, risperidone, aripiprazole, quetiapine, paliperidone, and olanzapine for the management of schizophrenia among adolescents aged 13 years or more. It is suggested that selection of specific agent should be based on the side effect profile [Table 6] and various other factors [Table 7]. Clozapine should be reserved for patients with treatment-resistant schizophrenia.

When prescribing antipsychotics, the clinicians need to explain the patient and the family members about the available options, possible side effects, need for monitoring, what to do in case the side effects are encountered, and behavioral measures required to minimize the side effects.

Doses of antipsychotic medication

In general, it is suggested that whenever an antipsychotic is to be given, it should be started in the lower doses and the patients should be closely monitored for emergent side effects. The doses should be gradually increased to the minimal effective therapeutic doses. It is noted that patients of Indian origin generally require lower doses compared to their counterparts from the West.

Route of administration

Only oral formulations of antipsychotics have been evaluated in children and adolescents. In general, use of depot antipsychotic medications is not recommended in children and adolescents. The Guidelines of American Academy of Child and Adolescent Psychiatry (AACAP) suggests that depot antipsychotics may only be considered in adolescents who have evidence of chronic psychotic symptoms in the form of documented history and a history of poor medication adherence.

Adequate antipsychotic trial

An adequate trial of antipsychotic is considered as use of maximum tolerable therapeutic doses for at least 6–8 weeks, except for clozapine, where the minimum duration of trial should be at least 3–6 months. If the patient does not show adequate therapeutic response, then a change in antipsychotic medication needs to be considered.

Monitoring of patients while receiving antipsychotics for side effects

All the patients receiving antipsychotics should be monitored throughout the treatment for EPS, i.e., drug-induced parkinsonism, dystonia, akathisia, and neuroleptic malignant syndrome. Patients should also be monitored for other side effects [Tables 8 and 9] and managed accordingly. EPS is more often seen in patients receiving FGAMs, especially high-potency antipsychotics such as haloperidol. EPS is also known to occur with SGAMs. Acute EPS is usually seen during the first few days or weeks of starting treatment and can manifest in the form of acute dystonia, pseudo-parkinsonism, and akathisia. Acute EPS is usually dose dependent and subsides with discontinuation of the offending agent. Unlike acute EPS, chronic EPS is not dose dependent and usually encountered with prolonged use (months to years) of antipsychotics and manifests in the form of tardive dyskinesia, tardive dystonia, and tardive akathisia. Chronic EPS often persists even after discontinuation of the offending medication. Initial step in the management of parkinsonism involves reduction in the dose of the offending agent. If reduction in dose does

Table 6: Risk of side effects with various antipsychotics based on the data in adolescents

Side effect	Antipsychotics
Weight gain	Olanzapine > clozapine > risperidone > quetiapine > aripiprazole
Hyperprolactinemia	Risperidone > olanzapine; clozapine-prolactin neutral; aripiprazole-reduced prolactin levels
Hyperglycemia	Risperidone > olanzapine
Rise in cholesterol levels	Quetiapine > olanzapine
Rise in triglyceride levels	Olanzapine > quetiapine
Hyperprolactinemia	Risperidone > olanzapine > ziprasidone
Extrapyramidal side effects	Ziprasidone > olanzapine > aripiprazole > risperidone

Table 7: Factors that influence the selection of antipsychotics

- Side effect profile of the agent
- Patient and family preference
- Cost of the treatment, affordability
- Clinician's familiarity with the use of particular antipsychotic medication in children and adolescents
- Psychiatric comorbidity
- Medical comorbidity
- Concomitant medications
- Past treatment response/nonresponse
- History of side effects
- Treatment resistance

not lead to resolution of symptoms or leads to inadequate control of symptoms or worsening of symptoms, then change to an antipsychotic medication with lower EPS potential needs to be considered. If a patient has responded to or are responding to particular antipsychotic medication and is experiencing parkinsonism symptoms, then a short course of anticholinergic medications may be considered. Acute dystonia is usually encountered after administration of first few doses of antipsychotics and respond to administration of parenteral anticholinergic or antihistaminergic medications. A short course of anticholinergic medications may also be useful in the prevention of acute dystonia. Management of acute akathisia involves reduction in dose and change of antipsychotic medication to an agent with lower EPS potential in a sequential manner. Severe akathisia in few patients may warrant the use of beta-blockers and benzodiazepines such as clonazepam or lorazepam.

Neuroleptic malignant syndrome (NMS) is an acute medical and psychiatric emergency, management of which involves stopping the offending agent, supportive measures and use of bromocriptine, amantadine, or dantrolene. Patients with NMS, who do not respond to these treatments, may benefit with ECT.

In patients who report sedation, wait-and-watch policy must be followed in the beginning; however, if this is not beneficial, then reduction in dosage must be considered. Patients receiving clozapine and chlorpromazine often experience dose-dependent anticholinergic side effects which improve with reduction in the dose of antipsychotic or addition of anticholinergic agent.

All antipsychotics lead to varying rates of sexual dysfunction, with higher rates noted for FGAMs than SGAMs. Sexual

Table 8: Monitoring of patients receiving antipsychotics

	Baseline	At 6 weeks	At 12 weeks	3-6 monthly interval	Monitor regularly throughout treatment, and especially during titration
Weight	Yes	Yes	Yes	Yes	
Height	Yes			Yes	
Waist circumference	Yes			Yes	
Pulse	Yes				
Blood pressure	Yes		Yes	Yes	
Fasting blood glucose	Yes		Yes	Yes	
HbA1c	Yes		Yes	Yes	
Lipid profile	Yes		Yes	Yes	
Review personal history for medical illnesses, especially diabetes mellitus, hypertension, dyslipidemia, cardiac abnormalities and seizures	Yes				
Review family history for medical illnesses, especially diabetes mellitus, hypertension, dyslipidemia, cardiac abnormalities and seizures	Yes				
ECG	Yes*				
Abnormal Involuntary movement disorder scale and neurological rating scale	Yes				Yes

*Monitor ECG of the patients with personal or family history of cardiac abnormalities, including sudden cardiac death, syncope, arrhythmias. HbA1c – Glycosylated hemoglobin; ECG – Electrocardiogram

Table 9: Management of other side effects

Adverse effect	Consider switching to another agent with lower risk	Lower the dose	Encourage healthy lifestyle measures	Add weight loss agents	Add specific corrective pharmacological agents
Tardive dyskinesia	✓				Vitamin E
Akathisia	✓	✓			Add benzodiazepines, beta-blockers, antihistaminic or anticholinergic agents
Constipation	✓				Behavioral changes Increase fluid and fiber intake in the diet Add stool softeners, laxatives
Dizziness/orthostatic hypotension	✓				Increase fluid intake Behavioral measures
Sedation	✓	✓			Wait for tolerance to develop
Hyperprolactinemia	✓	✓			Rule out other causes Add bromocriptine/amantadine/aripiprazole
Excessive weight gain	✓		✓	✓	
Glucose abnormalities	✓		✓	✓	Antihyperglycemic agents
Hypertension, tachycardia	✓	✓	✓	✓	Antihypertensives
ECG changes	✓		✓	✓	
Dyslipidemia	✓		✓	✓	Lipid-lowering agents
Electrolyte abnormalities	✓				Use corrective measures
Rise in liver enzyme levels	✓	✓			

ECG – Electrocardiogram

dysfunction with FGAMs and risperidone is related to increase in serum prolactin levels, which disrupts the hypothalamic–pituitary–gonadal axis. Females are considered to be more sensitive to hyperprolactinemia-related sexual dysfunction. First step in the management of sexual dysfunction involves reduction in the dose of antipsychotic medication, and if this fails, then a change in antipsychotic is needed. However, if a change of antipsychotic is not possible, then management of hyperprolactinemia with bromocriptine or amantadine may be considered.

As antipsychotics are considered to increase the prevalence of metabolic abnormalities, it is recommended that all the patients receiving antipsychotics must be closely monitored for side effects. AACAP and NICE guidelines have given specific recommendations for monitoring of patients on various antipsychotic medications. It is important to monitor the patient for metabolic abnormalities including the weight gain. SGAMs are known to cause significant weight gain, and significant rise in serum triglyceride levels is also seen in patients receiving various SGAMs [Table 6]. All patients must be evaluated for metabolic disturbance before starting of antipsychotics and then monitored [Table 8]. Frequency of monitoring can be increased in those with personal and family history of obesity, diabetes mellitus, dyslipidemia, hypertension, and/or cardiovascular disease.

However, in Indian setting, due to poor follow-up rates and inadequate resources at remote places, it may not be possible to monitor all the parameters regularly. In such situation, at least weight and fasting blood glucose levels should be monitored. Centers with resources may consider complete monitoring of metabolic parameters.

Besides the monitoring, all the patients and their family members must be informed about the need and importance of healthy lifestyle measures such as taking a healthy diet, regular exercise, and abstinence from smoking and alcohol. A close liaison must be maintained with endocrinologist and cardiologist to address the emergent issues. If a patient has significant weight gain or other metabolic disturbances with one antipsychotic medication, then he should be shifted to another agent with lower risk of gaining weight or causing metabolic disturbances. If a patient has significant metabolic disturbances, then these must be managed in liaison with the specialists. Gain in weight by more than 7% or emergence of hyperglycemia, hyperlipidemia, hypertension, or any other significant cardiovascular or metabolic side effect is considered an indicator for change in antipsychotic medication. However, before switching a review of entire course of the illness, other comorbid physical illnesses, side effect profile of medication which caused metabolic side effects and the potential side effects with medication to which patient is to be switch must be taken into account, before implementing a switch. If switching of antipsychotic is not feasible, then use of metformin or topiramate may be

considered, along with more intensive dietary and lifestyle modifications.

Use of antipsychotic medications is also associated with cardiac side effects such as orthostatic hypotension, tachycardia, and QTc prolongation. QTc prolongation is one of the dreaded side effects associated with use of antipsychotics and a QTc interval of more than 500 milliseconds is associated with increased risk of ventricular arrhythmias, known as “torsades de pointes,” which may lead to ventricular fibrillation and sudden cardiac death. Among the various SGAMs, ziprasidone is known to higher risk of QTc prolongation, and in terms of FGAMs, haloperidol in high doses, thioridazine and pimozide are associated with higher risk of QTc prolongation.

Hypotension is commonly seen with clozapine, risperidone, quetiapine, and chlorpromazine and is attributed to antiadrenergic properties of these drugs. The risk of hypotension can be minimized by initiating treatment with lower doses and very slow titration of medication. If a patient develops hypotension, then at the first step, a reduction in the dose of the offending agent is considered. If this does not lead to resolution of symptoms, then a change to antipsychotics with lower antiadrenergic properties must be considered. Other strategies such as use of stockings, increasing the salt intake, and use of fluid-retaining corticosteroid, i.e., fludrocortisone, are also useful in some of the patients.

Some patients receiving clozapine experience tachycardia due to anticholinergic activity and this can be managed with low-dose peripherally acting beta-blockers.

While using clozapine, hemogram must be monitored as per the established guidelines.

Response to treatment

Available evidence suggests that the use of antipsychotics in adolescents is associated with significant improvement in positive symptoms, with nonsignificant improvement in negative symptoms. Effect on antipsychotics on cognitive symptoms among adolescents has not been evaluated among the adolescents.

Nonresponse to treatment

As in adult patients, if a patient fails to respond to particular antipsychotic medication, compliance with medication needs to be evaluated, before considering a change in the medication [Figure 2]. If noncompliance or poor compliance is cause of nonresponse, then appropriate measures must be taken to ensure compliance with medication. If a patient does not respond to the medication even after ensuring proper medication compliance and giving medications in adequate therapeutic doses for 6–8 weeks, then change in medication be considered. If the patient fails to respond to two consecutive adequate trials (at least one of which is an

SGAM), then clozapine needs to be considered. At present, there is lack of evidence in terms of making recommendation for patients who fail to respond to clozapine. Based on the data from adults, ECT or combination of clozapine with another antipsychotic medication may be considered. However, the use of combination of two antipsychotic medications must be done, after explaining the patient and family members about lack of evidence for the same and possibility of risk of higher side effects.

Relapse prevention

Majority of the patients with schizophrenia require long-term treatment as there is high risk of relapse of symptoms with discontinuation of antipsychotics. In fact, compared to adults, higher proportion of children and adolescents with schizophrenia have chronic impairment, even while receiving continuous treatment. Patients who respond to treatment must be monitored from time to time to evaluate the course of the symptoms, side effect profile, psychosocial functioning, and medication adherence. During the stabilization phase, ideally, the same dose used during the acute phase must be continued. However, during the stable phase, minimum effective dose be used to minimize the risk of side effects. However, it is to be remembered that any change in the doses must be done slowly with close monitoring of symptoms.

Adjunctive medications

Although as a class of medications, antipsychotic agents remain the primary agents for management of schizophrenia in children and adolescents, management may involve use of adjunctive treatments such as with benzodiazepines (for anxiety, insomnia, akathisia, agitation, and catatonia), antiparkinsonian medications (for management of EPSs), antidepressants (for depression), and mood stabilizers (instability of mood and aggression). However, there is lack of data on use of these agents as adjuvant medications in children and adolescent with schizophrenia. Hence, if these have to be used, these may be used with proper rationale and for shortest possible duration after explaining the patient and/or the family members about the side effect profile and lack of supportive evidence. Prophylactic use of anticholinergics is not recommended; however, these can be given if patient develops EPSs in the lowest possible doses and for the shortest possible time. Prophylactic use of anticholinergic agents may be considered in patient with a past history of acute dystonias and those who are at risk of developing acute dystonia.

Electroconvulsive therapy

There is limited evidence for the use of ECT in children and adolescents with schizophrenia. Data from India

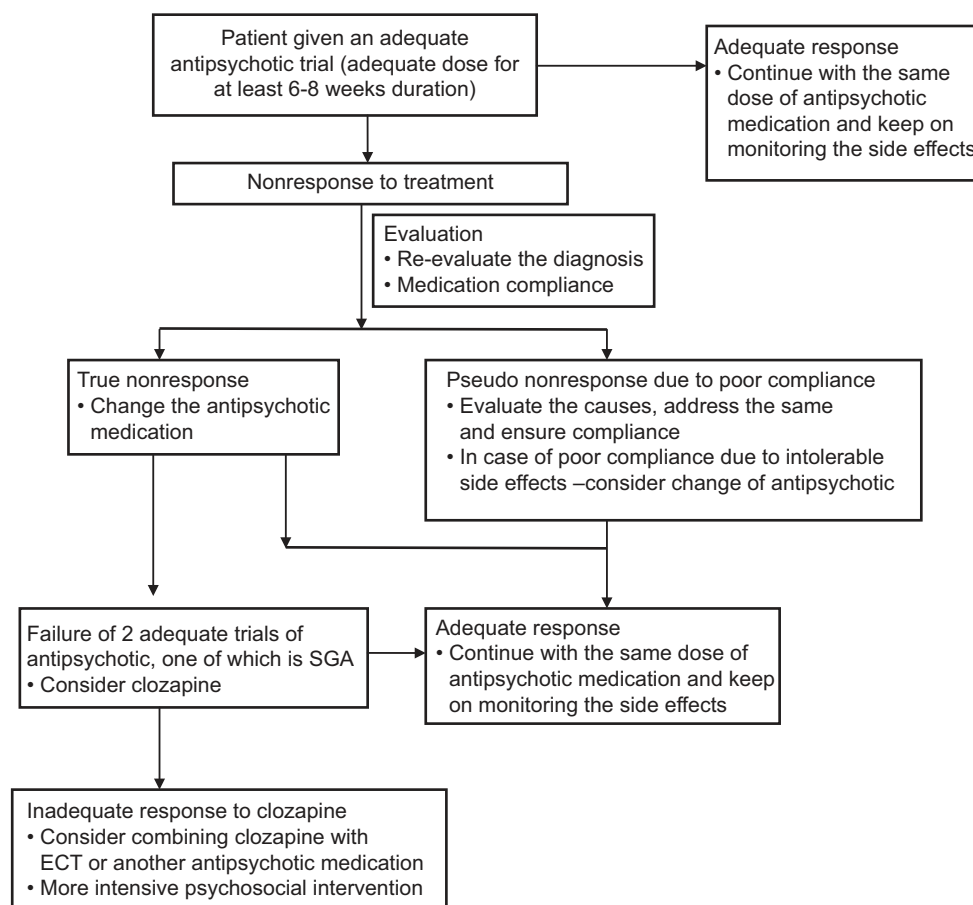


Figure 2: Evaluation of patient with non-response to antipsychotic medications

suggest that among adolescents, ECT is most commonly used in patients with schizophrenia, mainly for catatonic symptoms, and found to be effective.^[11,12] Various treatment guidelines including Indian Psychiatric Society Guidelines for the management of schizophrenia recommend use of ECT among adult patients with schizophrenia for catatonia, affective symptoms, need for rapid control of symptoms, presence of suicidal behavior endangering life of the patient, presence of severe agitation or violence which puts the life of others at risk, refusal to eat which puts the life of patient at risk, history of good response in the past, patients not responding to adequate trial of an antipsychotic medication, and augmentation of partial response to antipsychotic medication. Practice parameters of AACAP recommend that clinician must evaluate the risk and benefit of use of ECT against the risk of morbidity associated with the disorder and must consider the attitudes of the patient and the family and availability of the alternative treatment options before considering ECT in adolescents. In the Indian context, too, ECT may be considered with similar evaluation of risk and benefits for the patient. If ECT is considered, then proper informed consent must be obtained from the parents, after proper explanation of the possible cognitive side effects. ECT can be used in children and adolescents with catatonic symptoms, depression, and treatment-resistant schizophrenia. ECT if used in adolescents must also confer to the recommendations of the Mental Health Care Act, 2017.

Psychosocial interventions

Psychosocial interventions are integral part of management of schizophrenia. Various psychosocial interventions which have been found to be useful in the management of schizophrenia in adult patients include family interventions, cognitive behavioral therapy (CBT), cognitive remediation therapy (CRT), social skills training, individual supportive therapy, group therapy, vocational rehabilitation, case management, and use of community mental health teams and of crisis resolution teams. Occasional studies have also evaluated CRT, CBT, and family intervention/psychoeducation in patients with EOS, and the available data suggest that CRT is useful in the management of EOS. Studies which have integrated the components of problem-solving, psychoeducation, and family intervention have also shown the beneficial effect of the same in improving the outcome of patients with schizophrenia.

There is ample evidence from India too, which suggests that family intervention, rehabilitation, and other modalities such as community programs, yoga, and cognitive remediation are also useful in adult patients with schizophrenia. Based on these data, it can be said that same psychosocial interventions, which have been effective in adults, may also be effective in children and adolescents with schizophrenia and their parents/family members. The basic steps in providing psychosocial intervention involve

assessment of psychosocial factors involving the patient and the family. Based on the assessment and available resources, interventions need to be tailored to address the needs of patients and their parents/family members. Basic components of any kind of psychosocial intervention should include enhancing therapeutic alliance with the patient and the family, encouraging engagement of the patient and family members in the treatment, sharing information about various aspects of the illness, focusing on treatment adherence and healthy lifestyles, and offering emotional and practical support.

Psychoeducation

Psychoeducation of both patient and family members is an integral part of management of schizophrenia. The basic component of psychoeducation includes providing information about the disorder and the available treatment options to the patient and the family [Table 10]. Effort must be made to provide simple and brief explanation about the nature of the illness, available treatments, possible side effects which may be encountered, and duration of treatment. Use of technical jargon should be kept to minimum and clinical information need to be provided in the language in which patient and the parents/caregivers are most comfortable. Further, there should be no information overload for the participants, rather information needs to be passed on in piece-meal fashion, tailored according to the acceptability of the patient and the family members. During psychoeducation, patient and family must be given enough opportunity to ask questions and clarify their doubts and misconceptions about the illness. Diagnosis of schizophrenia in children is often traumatic for the parents and to the sufferer too; hence, enough time must be given to the parents and the patient to accept this painful fact. Many a times, parents blame themselves or their partner for the illness in the child. Efforts must be made that no blame is attached to any one member of the family. An important aspect of psychoeducation is also to emphasize the need for regular intake of medication. Before starting every session, feedback of the earlier sessions must be taken, and future sessions must be tailored according to the need of the patients and their parents.

Family interventions

Family interventions, mainly in the psychoeducational format, can be useful in patients with schizophrenia. These interventions can be provided in the informal or unstructured form, structured format, individual or group format, and as specific strategy or as integrated psychosocial treatments combined with components of other psychosocial treatments. The basic emphasis of the family intervention programs should be on regular treatment contact with emphasis on the need for regular medication adherence and providing emotional and practical support. Family-based interventions also focus on communication patterns to address the issue of expressed

Table 10: Basic components of psychoeducation

- Assess the knowledge of the patient and caregivers about etiology, treatment, and prognosis of the disorder
- Introduce the diagnosis of schizophrenia into discussion
- Discussing about various symptom dimensions
- Providing information about possible etiology
- Providing information about treatment in terms of available options, their efficacy/effectiveness, doses, side effects, duration of use
- Discuss importance of medication and treatment compliance
- Provide information about possible course and long-term outcome
- Discuss about problems of education, substance abuse, marriage etc.
- Discussing communication patterns, problem-solving, disability benefits
- Discussing possibility of relapse and how to identify the early signs of relapse
- Deal with day-to-day stress
- Improve insight into illness
- Identify expressed emotions and handle expressed emotions and improve the communication between the patient and other family members
- Enhancing adaptive coping to deal with persistent/residual symptoms

emotions. The family intervention programs should be designed in such a way these meet the need of the patients and the family.

Advise for lifestyle and dietary modifications

All the patients must be informed about the side effect of weight gain with SGAMs, and they must be advised to change their lifestyle (regular physical exercise, abstinence from smoking, alcohol, and use of other illicit drugs) including diet to minimize the risk of metabolic side effects and ensuing cardiovascular morbidity and mortality.

Supportive therapy

Supporting therapy in the form of empathetic listening of patient promotes therapeutic alliance. Other components of supportive therapy include support and advice, encouraging continued engagement, enhancing adaptive coping, treatment adherence, and healthy lifestyles. All the efforts focused on stress reduction are considered to be beneficial.

Cognitive behavioral therapy

CBT in psychosis aims to enhance the understanding about illness and improve insight into psychotic experiences, as well as to improve coping with residual psychotic symptoms. CBT also helps to reduce the distress associated with hallucinations and also reduces the degree of conviction and preoccupation with delusional belief. In general, confrontation and collusion are avoided and questions are framed in such a way that these help in gathering evidence in a non-judgmental manner. CBT also attempts to address the hopelessness and low mood, using similar principles as used for the management of depression.

Cognitive remediation therapy

CRT aims to improve the cognitive processes (i.e., attention, memory, executive function, and social cognition) by repeated practice of various cognitive tasks. Use of CRT

among adolescents with schizophrenia has been shown to improve planning ability and cognitive flexibility.

Rehabilitation

Rehabilitation programs in children and adolescents should be guided by the needs of the patients and families. This should also take cultural issues into account. The rehabilitation strategies are also guided by the resources available at particular center and the resources of the family. Many patients return to their school after resolution of symptoms of acute phase. They must be emotionally supported and based on cognitive deficits; cognitive remedial measures may be provided.

Other psychosocial interventions

Other psychosocial interventions which have been shown to be of some benefit for adult patients with schizophrenia include home-based care, support groups for caregivers, community-based interventions, and yoga. However, there is a need for further systematic research to evaluate the efficacy of these modalities for children and adolescents.

PHASES OF ILLNESS/TREATMENT

As for other age groups, management of schizophrenia in children and adolescents is divided into three phases, i.e., acute phase, stabilization phase, and stable or maintenance phase. However, it is important to remember that compared to adults, relatively higher proportion of patients belonging to children and adolescents age group will present in the prodromal phase. These patients also require proper assessment and management.

PRODROMAL PHASE

Patients in the prodromal phase may present with abnormalities in the domains of cognition, emotion, perception, communication, motivation, and sleep, rather than having clear psychotic symptoms. The important aspect of assessment of these patients is that, although all of them do not go on to develop psychotic disorders, compared to general population, these subjects have higher risk of conversion to florid schizophrenia and the nonspecific symptoms seen at this stage may have negative consequences on the cognitive, emotional, and social development of the person. Different studies suggest that the conversion rates range from 25% to 40%. Conversion to frank psychosis is predicted by family history of psychotic illness (especially in the first-degree relatives), longer duration of symptoms, higher severity of symptoms, reduced attention, higher degree of unusual thought content, suspiciousness/paranoia, high levels of depression, history of substance abuse (cannabis or amphetamines), recent deterioration in functioning, and presence of social impairment. The general recommendations for the management of this phase of illness include carrying out detailed assessment [Table 11] to document the symptoms in various domain and if possible stratification

of the possible risk. In terms of management, based on the available evidence, it is not possible to make any specific recommendations at this stage. In terms of management, in general, use of antipsychotics is not recommended. There is some evidence to suggest possible beneficial effect of omega-3 fatty acid and antidepressants, depending on the symptom profile. It is suggested that in the prodromal phase, patient must be provided need-based nonpharmacological management. There is some evidence to suggest that psychosocial interventions such as CBT, cognitive therapy, and stress management can improve functioning and symptomatology during the prodromal phase, although the active components of these treatments are not well understood. Additional components of management include psychoeducation of patient and family, enhancing the coping abilities of the patients to deal with psychotic symptoms and addressing the issues of stigma.

MANAGEMENT IN THE ACUTE PHASE OF TREATMENT

Patients in the acute phase of treatment usually present with florid psychotic symptoms in the form of hallucinations, language disturbances, disturbed thinking, delusions, and behavioral disturbances. They also have severe impairment in functioning in the form of difficulties in education or work. Children and adolescents experiencing acute phase can also be at risk of harming themselves or others. In view of florid symptoms, both patients and the family members are often under distress and struggle to accept the fact. The various aspects of management in the acute phase are included in Table 12.

MANAGEMENT IN THE STABILIZATION PHASE

Stabilization phase of treatment commences with reduction or remission of symptoms seen in the acute phase, and this phase of treatment usually lasts for about 6–12 months. The components of management during the stabilization phase are shown in Table 13. The main objectives of this phase are further reduction in the symptoms and consolidation of remission and prevention of early relapses. The main goals of the treatment are continuous engagement of patient and family, providing emotional support, stress reduction, and enhancing adaptation to life. The objectives and goals of management can be achieved by continuing antipsychotic medications which led to remission or reduction in symptoms, monitoring treatment response and side effects, and continuing with the psychosocial interventions. Antipsychotic medications should preferably be continued at the same dose for the next 6–12 months. Psychosocial interventions are focused on maintaining treatment engagement and adherence, providing support to the patients and their families to come to terms with the illness and returning to normal walks of their life, addressing the new issues while going back to the usual life, and addressing issues related to stigma. Specific and

Table 11: Management during the prodromal phase

Comprehensive assessment (psychiatric/medical/psychosocial)
Use of self-rated screening questionnaires
PQ-B
YPARQ-B
Prime screen-revised
Screen for prodromal symptoms of psychosis (PROD-screen)
Use structured interview schedules to assess the patient
IRAOS
BSABS
SPI-A
SPI-CY
SOPS
SIPS
CAARMS
FCQ
If required, consider psychodiagnostics
If required and feasible, consider detailed cognitive assessment
Stratification of risk
Management
Engage the patient
Monitor the mental state
Provide support and treat comorbidities
Providing need based nonpharmacological treatment
Provide information to the patient and parents about the possible risk
Enhancing the coping abilities of the patients to deal with psychotic symptoms, if these are present transiently or emerge in due course of time
Assess and address stigma
Do not use antipsychotic agents unless the patient meets DSM or ICD diagnostic criteria for a psychotic disorder

PQ-B – Prodromal Questionnaire-Brief; YPARQ-B – Youth Psychosis At Risk Questionnaire-Brief; IRAOS – Instrument for the retrospective assessment of onset of schizophrenia; BSABS – Bonn Scale for the Assessment of Basic Symptoms; SPI-A – Schizophrenia Proneness Instrument for Adults; SPI-CY – SPI Child and Youth; SOPS – Scale for prodromal symptoms; SIPS – Structured interview of prodromal symptoms; CAARMS – Comprehensive assessment of at-risk mental states; FCQ – Frankfurt Complaint Questionnaire; ICD – International Classification of Diseases; DSM – Diagnostic and Statistical Manual

elaborate psychosocial interventions can also be tried at this stage. Throughout the stabilization phase, patient treatment response, side effects, and medication adherence must be monitored.

MANAGEMENT IN THE STABLE PHASE

During this phase of illness, symptoms are usually less severe and stable. The clinical picture may be predominated by negative symptoms along with problems in cognitive, social, and occupational functioning. This phase basically involves carrying forward the gains achieved in the acute and stabilization phase of management. The main aims of this phase of management are maintaining or improving level of functioning, preventing recurrences of symptoms, promoting psychological/personal recovery, and rehabilitation of the patient. The management plan should be reviewed from time to time and necessary changes are made to improve the overall outcome of the patient. This phase involves determining the goals, continuing with further assessments, continuing with antipsychotic medications, monitoring and minimizing the side effects, carrying forward the ongoing psychosocial interventions, and adding further psychosocial

Table 12: Management in the acute phase**Comprehensive assessment (psychiatric/medical/psychosocial)**

Deciding on goals of treatment

Patients

- Eliminate/reduce symptoms of schizophrenia
- Promote safety, reduce risk of harm, reduce stress
- Improve functioning of the patient

Caregivers

- Minimize caregiver distress
- Offer help to enable them to cope with the illness in their relative

Both

- Develop a good therapeutic alliance and provide opportunities for patients and caregivers to actively engage in treatment
- Offer basic information and support tailored to needs of patients and caregivers

Decide about choice of treatment setting

Antipsychotic treatment

- Choice of drug: provide adequate information to the patient and parent/family members in terms of available choices and possible side effects
- Dose: start low, go slow
- Discuss duration of treatment
- Determining response or non-response

Use adjunctive medications when indicated

Use modified ECT if indicated

- Obtain opinion of another psychiatrist, provide adequate information to the patient and parent/family about the availability of the alternative treatment, possibility of cognitive impairment and obtain written informed consent before starting ECT

Psychosocial interventions relatively basic and mainly for the purpose of fulfilling the goals of treatment listed above

Planning for further treatment

ECT – Electroconvulsive therapy

Table 13: Management in the stabilization phase

Determining goals

Further assessment

Continuation of antipsychotic treatment

Continuation of psychosocial interventions started during the acute phase and addition of other psychosocial interventions as per the needs

Monitor the treatment response

Monitor side effects: investigations and assessment to be done as per the recommendations and need

Monitor treatment adherence

interventions for new emergent issues. Different components of this phase are shown in Table 14.

At every follow-up, progress of the patient needs to be reviewed, and feedback must be taken from the family and other available sources. Progress in the education and occupation needs to be reviewed and rehabilitation need to be planned to reintegrate the patient into the society. Frequency of contact can be determined based on the clinical state, the distance of the hospital from the patient's home, available social support, and the type of treatment being administered. In general, the frequency of follow-up can be reduced in this phase of treatment to once in 2–3 months. However, more frequent follow-ups need to be considered if the patient is going through any crisis or there are psychosocial issues which require attention. More frequent follow-ups also need to be considered if the

Table 14: Management in the stable phase

Goals of treatment

- Maintain or further improve the level of functioning in various domains
- Improve quality of life
- Rehabilitation
- Reintegration of patient into the society
- Facilitate personal recovery
- Prevent psychotic exacerbations/relapses
- Minimize the side effects of medication

Assessments and monitoring

- Assess the level of response, residual symptoms, and side effects
- Assessment for carrying out new psychosocial interventions

Re-evaluating/modifying the treatment plan

- Re-evaluate the needs of the patient and the family and modify the treatment plan as per the need
- Continue with further assessment: modify the management plan, to accommodate any new problems or demands of the patient and the caregivers

Antipsychotic treatment

- Draw a balance between minimum dose required to prevent relapse and the dose required to minimize the side effects

Psychosocial interventions

- Continue with the interventions started in the previous phases
- Evaluate the gains with the psychosocial interventions done till now and modify the psychosocial interventions to further improvement
- Evaluate the ongoing psychosocial interventions for any possible change required
- Add new strategies to improve the outcome

Monitoring for response, side effects, and treatment adherence

Early intervention for relapses

- Educated the patient and the relatives to recognize early symptoms of a relapse
- Provide information as to what to do, in case there are signs and symptoms of an impending relapse
- Provide information about how to access the emergency services
- Increasing the dose of antipsychotics
- Addressing the emergent psychosocial stressor, if any
- Considering brief admission
- Increasing the frequency of visits to the clinic/home visits

patient or family desires so. If there is emergence of new psychosocial issues, then these must be addressed.

The goals of management during the stable phase of treatment are to maintain or further improve the level of functioning in various domains, improve quality of life, and facilitate personal recovery. Psychotic exacerbations need to be effectively treated. Side effects of the medications should be monitored and managed effectively.

As time relapses, the nature of the illness, problems faced by the relatives, needs of the patient and the family, and previously determined targets are all expected to change. Regular contact, awareness, and monitoring are needed to detect these changes. Ongoing assessment is thus essential. It allows those modifications to be made in the treatment plan, which are required to accommodate any new problems or demands that may have arisen.

The dose of the antipsychotic to be used during this phase needs to be individualized. While determining the dose,

Table 15: Issues related to special situations

Special situation	Strategies
Suicidality in schizophrenia	High-risk management need to be instituted, and if feasible, the patient needs to be admitted Adequate control of psychotic symptoms and associated depression Clozapine may be preferred for patients who have multiple suicide attempts and those who have persistent suicidal ideations Psychoeducation need to focus on warning signs of suicide Patients experiencing severe distress due to a feeling of loss, stigma, etc., must be provided psychological support and monitored closely
Violence and aggression in schizophrenia	At every visit, assess the patient for violence and dangerousness, especially during the acute phase of illness Consider inpatient care if the patient is found to have serious threat for violence or exhibits violence Use Injectable antipsychotics like haloperidol or lorazepam for management of violence and aggression
Comorbid substance use disorders	Presence of substance use disorder is often associated with overall poor outcome of illness Aim for abstinence from the substances or at least harm reduction Use detoxification regimen and pharmaco-prophylaxis for substance use disorders as per the requirement Add psychosocial interventions specifically used for substance use disorders: prevention counseling, cognitive behavioral interventions, and motivation enhancement treatment Monitor continuously for relapse of substance use disorder
Depression	Consider other differential diagnoses (organic conditions, negative symptoms, antipsychotic associated side effects such as dysphoria, akinesia and akathisia, schizoaffective depression, stress-related reactions, and an impending psychotic episode) Data from adults suggest that SGAMs are superior to FGAMs in their antidepressant efficacy Clozapine may be particularly effective in patients at high risk for suicide Avoid antidepressants during the acute phase of psychotic illness, antidepressants useful in post-psychotic depression ECT can be helpful
Catatonia	Consider all possible differential diagnosis for catatonia, investigate as per the need Initial management may involve use of benzodiazepines, especially lorazepam, which leads to symptomatic relief in significant proportion of cases In case the catatonia does not respond to benzodiazepines or relapse after stopping benzodiazepines, ECT need to be considered
Negative symptoms	Rule out secondary negative symptoms There are no treatments with proven efficacy for primary negative symptoms, although some benefit has been reported with clozapine and amisulpride in adults Psychosocial interventions: social skill training, token economy
OCS in schizophrenia	OCD/OCS: can be seen in any phase of treatment (prodrome, acute phase, post-psychotic phase) and may be treatment emergent (clozapine, olanzapine, and risperidone) If the OCS/OCD appear to be part and parcel of schizophrenia, initially treat with antipsychotics only If the OCS/OCD is considered to be treatment emergent: reduce the dose of antipsychotic, change of antipsychotic, use antiobsessional agents (clomipramine and fluvoxamine) CBT in the form of exposure and response prevention has also been tried with beneficial effects in adults
Comorbid physical illnesses	Thorough assessment for possible physical illnesses and investigations must be done as per the need and feasibility Consider comorbid physical illnesses and concomitant medications while selecting the treatment setting and antipsychotic medication per se Continuous monitoring of both mental and physical health during all the phases of treatment
TRS	Proper ascertainment that the patient has failed two adequate trials (dosage, duration, and adherence) Consider other possible causes of nonresponse (noncompliance, adverse effects, comorbid conditions such as substance misuse) before considering treatment refractoriness Clozapine has been reported to be beneficial among patients with treatment resistant schizophrenia
Clozapine -resistance	Psychosocial interventions such as cognitive therapy, family treatment, assertive outreach or crisis intervention are also beneficial There is some evidence in adults to suggest that combining ECT with clozapine improves the outcome of patients who do not respond to clozapine alone Evidence for combination of clozapine with other antipsychotics, antidepressants, mood stabilizers is limited even in adults and not convincing
Difficult to treat schizophrenia	Factors which make the patient difficult to treat include: inadequate response to antipsychotic, problems of adverse drug effects, poor medication compliance, comorbidities, treatment failure and relapse on adequate drug dosages Psychosocial factors influencing medication compliance must be evaluated and addressed Issues related to adverse effects must be addressed Select antipsychotic by taking medical and psychiatric comorbidities into account

TRS – Treatment-resistance schizophrenia; FGAMs – First-generation antipsychotics; SGAMs – Second-generation antipsychotics; OCD – Obsessive-compulsive disorder; OCS – Obsessive-compulsive symptoms; ECT – Electroconvulsive therapy

balance has to be drawn in terms of minimum dose required to prevent relapse and the need to minimize the side effects. Reduction in the dose of antipsychotics may be considered in patients who are clinically stable and do not have any positive symptoms. If dose reduction is considered, then the doses need to be reduced gradually at the rate of about 20% every 6 months still a minimum effective dose is reached.

Reduction of dose/withdrawal of antipsychotic medication may be undertaken gradually while regularly monitoring signs and symptoms for evidence of potential relapse. Following withdrawal from antipsychotic medication, monitoring for signs and symptoms of potential relapse needs to continue for at least 2 years after the last acute episode. Any re-emergence of symptoms is to be immediately treated.

Duration of treatment will depend on multiple factors and this need to be individualized. In general, it is suggested that patients experiencing first-episode of schizophrenia need to receive maintenance treatment of 1–2 years duration. Patients who have history of multiple episodes or exacerbations need to receive maintenance treatment for 5 years or longer after the last episode. Patients with evidence of aggression or suicide attempts should receive treatment for longer period or lifelong. The usual indications for use of lifelong antipsychotic medications include history of multiple relapses while on treatment, evidence of relapses when the medications are tapered off, history of two episodes in the last 5 years, evidence of suicidal attempts, presence of residual psychotic symptom, family history of psychosis with poor outcome, and presence of comorbid substance dependence.

The psychosocial interventions started in the previous phases of treatment must be carried forward and modified as per the needs.

In a country like India, facilities for vocational rehabilitation are very limited. If the patient is willing to continue with his education or is continuing with his education, then efforts must be made to improve his outcome. If patient is not on any job, then further evaluation needs to be done to identify their suitability for particular job and they should be encouraged to search for a job for themselves. If the patient is already working and facing any problems at the workplace, then efforts must be made to address the same. If there is a need for rehabilitation, then culture-specific rehabilitation program need to be considered.

The management plan should be organized in such a way that any relapse of symptoms can be addressed at the earliest. Patients and relatives should be enabled to recognize early symptoms of a relapse and should be informed about the need for early intervention when there is evidence of an impending relapse. They need to be informed about how to access to treatment facilities such as emergency services or inpatient settings, in case patient is on the verge of a relapse. Crisis interventions in the form of brief admissions or frequent home visits need to be adopted, whenever feasible.

MANAGEMENT IN SPECIAL SITUATIONS

Management of schizophrenia often leads to certain clinical situations which often influence treatment decisions. Management of these situations is summarized in Table 15.

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Conflicts of interest

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