BAP GUIDELINES FOR THE MANAGEMENT OF SCHIZOPHRENIA

1st Edition 2022

বাংলাদেশ এসোসিয়েশন অব সাইকিয়াট্রিস্টস (বিএপি)
Bangladesh Association of Psychiatrists (BAP)

Scientific Partner

SUN PHARMA
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GENERAL PHYSICIANS

General physicians from different organizations who took part in the focus group discussion and shared their knowledge about the management of schizophrenia.

PATIENTS/CAREGIVERS

Patients and their caregivers who took part in the focus group discussion and shared their views.

FOCUS GROUP DISCUSSION FACILITATORS

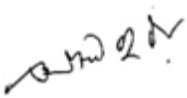
Dr. Md. Harun Ul Morshed and his team

Preface to the First Edition

Schizophrenia is a major psychiatric disorder, which is chronic and debilitating, negatively impact the quality of life and functioning and associated with significant morbidity and mortality. The Bangladesh Association of Psychiatrists (BAP) felt the need to develop a management guideline for schizophrenia for psychiatrists and also for physicians working in non-specialized settings to improve clinical practice while recognizing, assessing, diagnosing and treating schizophrenia patients.

This guideline is based on available evidence on epidemiology, diagnosis and treatment of schizophrenia obtained mainly through desk review of established guidelines. The suggestions in this guideline represent the view of BAP, arrived at after careful consideration of different evidence. However, we expect that the users will exercise their judgement, alongside with the individual needs, preferences and values of the patients.

I want to thank everyone who worked rigorously during this guideline development process. I believe this guideline will greatly help to improve mental health care practices in Bangladesh and consequently our patients' lives.



Prof. Dr. Md. Waziul Alam Chowdhury
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Acknowledgement

We would like to express our sincere gratitude towards the BAP members for their continued support and encouragement; the psychiatrists, general physicians, patients and their caregivers who participated in focus group discussions and gave their valuable feedback and time; the health care professionals involved in the management of schizophrenia. We are immensely thankful to Sun Pharmaceutical (Bangladesh) Ltd. for their contribution as the scientific partner. They offered all kinds of logistic and financial support for the development of the guideline.

Sun Pharmaceutical (Bangladesh) Ltd. sincerely salutes this incredible achievement of Bangladesh Association of Psychiatrists (BAP) for successfully and efficiently developing the guidelines for the management of schizophrenia for the first time in Bangladesh. It was never an easy task to effectively formulate Bangladesh specific schizophrenia treatment guideline in congruence with various international guidelines.

It was the huge effort of the working committee, technical advisory committee, team of focused group discussion and the leaders of BAP who made this enormous endeavor possible within such a short period of time.

Sun Pharma is extremely proud and grateful to be a part of this novel initiative and is immensely thankful to BAP for bestowing them with this opportunity.

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Symbols and Abbreviations

BPRS	Brief Psychiatric Rating Scale
CBC	Complete Blood Count
CBT	Cognitive Behavioral Therapy
CBTp	Cognitive Behavioral Therapy for Psychosis
DGHS	Directorate General of Health Services
ECG	Electrocardiography
ECT	Electroconvulsive Therapy
EPS	Extrapyramidal Symptoms
ERP	Exposure and Response Prevention
FEP	First Episode Psychosis
FGA	First Generation Antipsychotic
HbA1c	Hemoglobin A1c
LAIs	Long Acting Injectables
LFTs	Liver Function Tests
NIMH	National Institute of Mental Health
NICE	National Institute for Health and Care Excellence
PANSS	Positive and Negative Syndrome Scale
rTMS	Repetitive Transcranial Magnetic Stimulation
SGA	Second Generation Antipsychotic

Contents

Section I

Background

Introduction

Schizophrenia is a chronic major mental illness of multifactorial (heterogeneous) etiologies characterized by disturbance of thinking, emotion, perception and behavior. The predominant clinical features in acute schizophrenia are disorganized speech, delusions, hallucinations and interference with the flow of thoughts. These features are often called positive symptoms. In chronic schizophrenia main features are very different, consisting of apathy, lack of drive, under activity, slowness and social withdrawal. These features are often called negative symptoms. There are multiple genetic and environmental factors that contribute to the causation of schizophrenia. Life events, substance use, treatment adherence have important roles in the course of the disease.

Core symptoms

- Delusions
- Hallucinations
- Disorganized speech (e.g., frequent derailment or incoherence)
- Grossly disorganized or catatonic behavior
- Negative symptoms (alogia, avolition, anhedonia, affective flattening, social withdrawal)

* Please see "Glossary" for ICD-11 and DSM-5 diagnostic criteria for schizophrenia

Epidemiology

Prevalence of schizophrenia is generally 1.0% around the globe with some variation found in different studies, population and geographical areas. In general, schizophrenia is equally prevalent in men and women. The onset is earlier in men than in women. The male female ratio is approximately 1.4:1. The ratio tends to fade as age increases, especially after 40 years. The peak ages of onset are 10 to 25 years for men and 25 to 35 years for women. Usually, onset of schizophrenia before age 10 years or after age 60 years is rare. When onset occurs after age 45 years, the disorder is characterized as late-onset schizophrenia.

In Bangladesh, National Survey on Mental Health (2018-19) revealed that community prevalence of schizophrenia spectrum and related disorders was 1.0%. But urban preponderance was found to be 1.4% while it was 0.8% in rural areas. Besides, schizophrenia spectrum disorders among children and adolescents were 0.2%.

Rationale

National Mental Health Survey Bangladesh, 2018-19 reported that overall prevalence of mental disorders among 18 years and above was 18.7% and among them schizophrenia spectrum disorders was found to be 1% (only schizophrenia was found 0.4%). The local health bulletin, DGHS morbidity report stated that schizophrenia has the highest number of admitted patients in National Institute of Mental Health (NIMH) Dhaka (43.1%) and Pabna Mental Hospital (40%) in the year 2020. According to the Global Burden of Disease Study, schizophrenia causes a high degree of disability, which accounts for 1.1% of the total DALYs (disability-adjusted life years) and 2.8% YLDs (years lived with disability). Stigma related to mental illness is a widespread issue in Bangladesh which is a major impediment towards help-seeking for mental disorders; however, the treatment gap is small for severe mental disorders.

It has emerged from focus group discussions that general physicians are not trained and skilled enough to diagnose and manage schizophrenia. Also, patients delay in seeking help and there is no clear referral system at work in Bangladesh. Till date, no single uniform management guideline for schizophrenia has been published in Bangladesh; so, Bangladesh Association of Psychiatrists (BAP) felt the need to develop a national clinical management guideline for the psychiatrists and for other physicians that can be widely incorporated at all levels of health care services from the community to tertiary.

Features of this guideline

• The concept, assessment, management and referral pathways are clearly described here.

• A nationwide 5W service mapping (Who's doing What, Where, When and for Whom) for management of schizophrenia are included in this guideline making it user friendly for psychiatrists and other physicians which will help in developing a rationale for liaison psychiatric service.

• The evidence-based principles of management plan were developed here after considering country context, cultural compatibility and available resources.

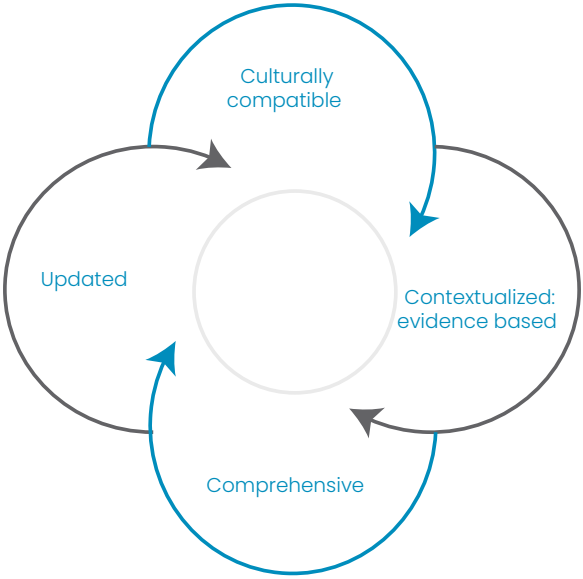
• Management for special population (pregnant & lactating mother, persons with physical comorbidity, etc.), special presentations and side effects of medication are included in this guideline.

• This guideline can be used for inpatient, outpatient and emergency settings.

• A comprehensive management plan including follow up and compliance issues are also discussed here.

• The guideline will be updated periodically.

Objectives



The objective of this guideline is to provide clear, concise and uniform information to all psychiatrists as well as other physicians on the current concept in the management of schizophrenia considering our country's context. Since schizophrenia is mostly managed by psychiatrists, this guideline provides necessary directives and primary management algorithm along the referral pathways for the general practitioners and physicians other than psychiatrists. Particular emphasis was given to make this guideline easy to be followed by psychiatrists to ensure advanced and updated management of schizophrenia, as well as a primary care model for physicians working in settings with limited resources.

Target users

Psychiatrists

- Recommended and updated management guideline for clinical practice
- Covers various aspects of schizophrenia
- Management guideline for special population and presentations

Physicians in non-specialized settings

- Primary assessment and management guideline of schizophrenia [what to do and what not to do]
- Referral pathway [when, where and how to refer]

Section II

Methodology

Methodology

This guideline has been developed after considering the desk review of updated clinical practice guidelines from several authorities like American Psychiatric Association (APA), National Institute for Health and Care Excellence (NICE guidelines), Schizophrenia Management Guidelines of Indian Psychiatric Associations, The World Federation of Societies of Biological Psychiatry (WFSBP), Guidelines for the Biological Treatment of Schizophrenia, etc. Working committee considered expert consensus, clinical experience and the findings from the focus group discussions (FGD) with the psychiatrists, general practitioners and persons with living experience of schizophrenia in Bangladesh.

Treatment recommendations used in this guideline are developed by considering the efficacy of each treatment modality across various phases of illness as well as safety and tolerability obtained from levels of evidence from various types of studies.

Definition of levels of evidence criteria used in schizophrenia treatment recommendations

Level	Evidence	BAP evidence gathering
I	Systematic review/meta-analysis of all relevant randomized controlled trials	Obtained from desk review
II	One or more properly designed randomized controlled trial	
III	Well-designed prospective trial (non-randomized controlled trial); comparative studies with concurrent controls and allocation not randomized; case-controlled or interrupted time series with a control group	
IV	Case series, either post-test or pretest/post-test	
V	Expert opinion	Consensus among experts, focus group discussion with psychiatrists, general practioners, patients and/or carers

Section III

Management

Assessment

A comprehensive assessment of the patient should include detailed psychiatric history, mental state and physical examination, and necessary laboratory investigations. Treatment history, comorbidity, cognition, abnormal motor behavior, positive and negative symptoms, substance use, risk of suicide and aggressive behaviors, functional impairment and psychosocial support are some of the areas that should be covered while assessing the patient. Neuroimaging and cognitive testing may help to rule out organic etiology of alternatives, such as schizophrenia-like manifestations of other disorders affecting brain function.

Basic Assessment

Comprehensive assessment of patient

Complete history with information from all possible sources
Family history of schizophrenia/psychosis

Areas to be evaluated

Symptom severity, duration and impact
Positive and negative, depressive and cognitive symptoms
Physical comorbidity and ongoing medications
Treatment history, compliance and adherence
Comorbid substance misuse including tobacco
Suicidal risk and risk of harm to self and others
Level of functioning
Socio- economic condition of the patient including stigmatization

Mental state examination

Thorogh assessment of the mental state-
Appearance and behaviour (including eye contact and motor activity)
Speech
Mood and affect
Thought
Perception
Cognition
Judgement
Insight

Assessment of caregiver/s

Knowledge and understanding of the illness
Attitudes and beliefs regarding treatment

Physical examination

Weight, body mass index, blood pressure, pulse, temperature, etc.

Basic investigations

Complete blood picture (CBC)
Blood sugar, HbA1c, lipid profile
Liver and renal function tests
Urea and electrolytes
Urine RME
Electrocardiogram (ECG)

Additional/optional assessment

Use of standardized rating scales to rate different aspects of the illness (e.g., PANSS, BPRS).
Psychological testing for cognitive functions.
Neuroimaging especially in those with first-episode psychosis, neurological signs, non-response to treatment and elderly patients.

Biological treatment

Antipsychotic drugs are the primary treatment for schizophrenia.
There is well-established evidence for their efficacy in the treatment of different phases of schizophrenia. Antipsychotics are used for the treatment of acute and chronic episodes, maintenance phase, relapse prevention, emergency treatment of acute behavioral disturbance. They are available as oral, intramuscular (IM), intravenous (IV) preparations and long-acting depot IM preparations.

General principles of prescribing antipsychotics

Dos	Don'ts
Lowest possible dose should be used at the beginning of treatment	Do not use high dose at the beginning of treatment
Increase dose after 1-2 weeks of initiating treatment, if needed	Do not use antipsychotics for sedation
Use of a single antipsychotic is recommended (apart from exceptional circumstances)	Do not use multiple antipsychotics at the same time (apart from exceptional circumstances)
Closely monitor the patient to see any side effects	
Routine use of anticholinergic medication can be considered for first generation antipsychotics	

Selection of antipsychotics

There is no difference in efficacy between first- and second-generation antipsychotics in the treatment of schizophrenia.

Clinical evidence summary (Level 1) suggested there were no clinically significant differences in efficacy between the oral antipsychotic drugs examined (FGA and SGA) for first episode psychosis, acute exacerbation or relapse prevention. The only exception is clozapine, which is more efficacious than any other antipsychotics in patients with treatment resistant schizophrenia. The choice of antipsychotic is guided by potential benefits and side effects profile which should be discussed with the patient/caregiver.

Factors tthat influence selection of antipsychotics

- Clinical presentation
- Previous treatment response
- Affordability and availability
- Side effects profile
- Patient profile – age, sex, body weight
- Special situation – pregnancy, lactation, etc.
- Psychiatric co-morbidity
- Medical co-morbidity
- Preferred route of administration
- Drug-drug interaction
- Non-adherence
- Treatment resistance

Stages of treatment

The pre-psychotic or prodromal stage

Before the emergence of positive psychotic symptoms that qualify a formal diagnosis of schizophrenia or first episode psychosis (FEP), some people show a prolonged period of attenuated or sub-threshold symptoms and increasing disability. This stage is commonly termed the 'prodrome' in retrospect, and the ultra-high-risk mental state or at-risk mental state (ARMS) prospectively. ARMS typically affects young people, usually aged between 14 and 35 years.

The pre-psychotic or prodromal stage can be associated with structural brain changes, mild or non-specific symptoms of psychosis, neurocognitive deficits and high propensity towards progression to first episode psychosis.

Rationale for Intervention

A significant portion of individuals having ultra-high-risk mental state or at-risk mental state will eventually develop psychotic disorders (22% at 1 year and 36% at 3 years). So proactive interventions are worthwhile.

Proactive intervention could result in attenuation of psychotic symptoms and delay or even prevent the onset of psychosis in some individuals.

Many people with at risk mental state may engage in self-harm or have suicidal ideation. This vulnerable group can be saved through prior intervention.

Suggested Interventions

Among the strategies investigated, CBT showed benefit in most cases followed by low-dose antipsychotics. Family therapy, needs-based support is also helpful.

Principles for pharmacotherapy for at-risk mental state (ARMS)

- This should be treated as off-label prescribing
- The prescription should be treated as a short-term, individual trial
- Very low doses should be used, even lower than used in first episode psychosis
- Expected benefits and potential side effects should be explained to the patient
- It should be prescribed by specialist psychiatric services, such as an early intervention team
- Individual CBT should always be considered as an acceptable alternative

First episode psychosis

First episode psychosis is defined as one week or more of sustained positive symptoms above the psychosis threshold for delusions and hallucinations in particular.

Principles of management

- In first episode psychosis, treatment with antipsychotics should be introduced with great care due to the higher risk of extrapyramidal symptoms (EPS).
- Early intervention in psychosis, services should be accessible to all people with first episode or first presentation of psychosis, irrespective of the person's age or duration of untreated psychosis. SGA is preferred due to low EPS.
- Metabolic parameters need to be closely controlled during treatment with antipsychotics. Skilled nursing care, a safe and supportive environment, and liberal doses of benzodiazepines may be essential to relieve distress, insomnia and behavioral disturbances secondary to psychosis.
- Early intervention in psychosis, services should aim to provide a full range of pharmacological, psychological, social, occupational, and educational interventions for people with psychosis according to the availability of service.

Treatment of acute phase

Most patients in this stage are likely to exhibit florid psychotic symptoms such as delusions or hallucinations, disorganized thinking and behavioral disturbances. Their functioning may be severely impaired and a few can be at risk of harming themselves or others. Additionally, both the patient and the family might have considerable difficulty in coming to terms with the illness.

Acute phase usually lasts from 4 to 8 weeks. The goals of treatment during acute phase are to eliminate or reduce symptoms of schizophrenia, promote safety, reduce risk of harm, reduce stress and improve level of functioning. Management begins with comprehensive psychiatric, medical and psychosocial assessment followed by decision on treatment setting and drug choice. Developing an alliance with the patient and family, offering basic information and support, formulating short- and long-term treatment plans and connecting the patient with appropriate healthcare services for further management are also important. While initiating treatment, drug choice, dose and route of administration are needed to consider.

Key recommendations for drug treatment

- Select drug after considering the factors mentioned in Page 23
- Start antipsychotic at lower end of the dose range
- Titrate dose within therapeutic range
- Target to achieve optimum dose by 4 weeks
- Monitor for effects and side effects
- Ensure adherence
- Decide on response and non-response

Treatment during maintenance phase

In the maintenance phase, the illness is in a relative stage of remission. The goals of treatment are to prevent psychotic relapse and improve level of functioning. During the maintenance phase of treatment, continue the same antipsychotic medication patient has responded to during the acute phase, following the same principles of acute episode.

Monitor and record the followings regularly and systematically throughout the treatment

- Efficacy
- Adverse effects of treatment
- Adherence
- Weight, BMI
- Pulse and BP
- Fasting blood glucose, HbA1c, blood lipids
- Nutrition, diet and physical activity

Key recommendations during maintenance phase

- After a single episode, continue antipsychotic medication for 1-2 years
- After multiple episodes, continue antipsychotic medication for at least 5 years
- Drug withdrawal should be gradual; antipsychotic discontinuation syndrome develops in up to 50% patients. Abrupt stoppage can result in psychotic relapse
- Consider depot formulation during maintenance phase, if adherence is a problem
- Consider psychosocial interventions, if available and affordable

Treatment-resistant schizophrenia (TRS)

The rates of primary treatment resistance at the onset of the illness have been found to be up to 23%. In some cases, treatment resistance develops over time, after an initial response to treatment. In schizophrenia treatment resistance is defined as a failure to respond to two trials of antipsychotic medications, one being from the second generation, of adequate dose and duration. Here response means more than 20% reduction of the symptoms, adequate dose means the midpoint of the therapeutic range and adequate duration means 6 weeks for each medication.

Clozapine for treatment-resistant schizophrenia

There is consistent evidence that clozapine is the most effective antipsychotic for TRS with a response rate found to be 30–75%. Given the clear superiority of clozapine over other agents, it is widely considered as the treatment of choice for people with TRS, and recommended that clozapine can be initiated within 6-12 months of treatment resistance.

Initial work-up for clozapine treatment

To screen for risk factors and provide a baseline parameter for future comparison, carry out physical examination and basic investigations (see page 20).

Mandatory blood monitoring

Regular full blood count weekly for the first 18 weeks and then every 2 weeks for the remainder of the year. After that blood monitoring is usually done monthly.

Summary of Clozapine Treatment

- Treatment with clozapine should be well-informed, individualized. Initial laboratory work-up, dose titration and monitoring of blood and screening for other side effects must be ensured.
- A trial of clozapine should be started with minimal delay, preferably within 6-12 months of treatment resistance.
- Clozapine monotherapy should continue for at least 6 months for an adequate trial.
- Treatment-emergent side effects should be monitored and managed proactively to maximize tolerance and reduce the risk of discontinuation.
- Plasma level of clozapine can be estimated to optimize dose (particularly in smokers and the elderly), check adherence or in case of problematic side effects.
- The dose should be gradually tapered over at least 1–2 weeks if clozapine is discontinued.
- If clozapine is stopped abruptly, a patient's physical and mental state should be monitored for withdrawal symptoms and rebound psychosis, particularly in the first week.
- If clozapine therapy is interrupted for more than 48 hours, it must be restarted at a dose of 12.5–25 mg/day.
- Augmentation of clozapine should be considered after at least 3 months of optimized clozapine monotherapy.
- An adequate trial of clozapine augmentation with another antipsychotic should be at least 8-10 weeks in duration.
- An agent for clozapine augmentation should be chosen considering its complementary receptor profile to clozapine, and resultant burden of side-effects.

Suggested options for augmenting clozapine (not in the order of preference)

Amisulpride (400–800 mg/day)

Aripiprazole (15–30 mg/day)

Haloperidol (2–3 mg/day)

Lamotrigine (25–300 mg/day)

Risperidone (2–6 mg/day)

Sulpiride (400 mg/day)

Topiramate (50–300 mg/day)

Sodium valproate (400–800 mg/day)

*Adapted from The Maudsley Prescribing Guidelines in Psychiatry, 14th edition

Other strategies in treatment-resistant schizophrenia

- **High-dose antipsychotic medication for treatment-resistant schizophrenia**

There is no evidence that higher doses were more effective for schizophrenia in general or for treatment-resistant illness.

- **High-dose olanzapine for treatment-resistant schizophrenia**

A systematic review and meta-analyses found clozapine to be superior to olanzapine for the treatment of positive and negative symptoms, though no significant differences between the two medications on dropout rates or total PANSS scale score were found. So high dose of olanzapine can be considered as an alternative to clozapine in TRS.

Combined non-clozapine antipsychotic medications for treatment-resistant schizophrenia

While antipsychotic augmentation was found to be superior to monotherapy with regard to total symptom reduction in some studies, there is a paucity of well-designed RCTs investigating treatment response for augmentation of non-clozapine antipsychotic combination.

Alternatives to clozapine

In situations where clozapine cannot be used because of intolerable side effects or the patient refuses to take the medication or comply with the mandatory monitoring, alternative treatments can be tried. Many of the treatments listed below are experimental and long-term data on their efficacy and safety/tolerability are lacking. So primary literature should be considered before their use.

Alternatives to clozapine (not in the order of preference)
Aripiprazole (15–30 mg/day)
Risperidone LAI (50/100 mg)
Olanzapine + Risperidone (variable dose)
CBT
ECT
Donepezil (5–10 mg/day) + Antipsychotic
Ondansetron (8 mg/day) + Antipsychotic
Celecoxib + Risperidone (400 mg + 6 mg/day)
Allopurinol (300– 600 mg/day) + Antipsychotic
Riluzole (100 mg/day) + Risperidone up to 6 mg/day

*Adapted from The Maudsley Prescribing Guidelines in Psychiatry, 14th edition

Combining antipsychotics

The main clinical reason for combining antipsychotics is to improve residual psychotic symptoms. There is limited evidence for the efficacy of combination treatment. On the contrary, combination of antipsychotics is associated with increased side effect burden. Regular combined antipsychotic medication should not be prescribed routinely, except for short periods when switching from one antipsychotic medication to another. In some situations, however, combination therapy can be judiciously used.

Some indications for combining antipsychotics	
Indication	**Suggested combination**
To mitigate metabolic side effects	Antipsychotic + Aripiprazole
To counter hyperprolactinemia	Antipsychotic + Aripiprazole
To manage agitation or anxiety	Antipsychotics + Quetiapine/Olanzapine *
Poor response to clozapine	Clozapine+ Amisulpride/Aripiprazole/Risperidone, etc.

* Level 3 evidence

Augmentation strategies

There is limited evidence for using augmentation strategies (i.e., the addition of a second drug not licensed for the treatment of schizophrenia after non-response to the prescribed antipsychotic) in the treatment of schizophrenia. Some open labeled efficacy-focused study reported significantly decreased total symptoms in augmentation group. As there is lack of high-quality evidence for superior efficacy of augmentation for non-clozapine antipsychotics, we recommend using them only after much consideration and on individual case basis.

Some indications for augmentation	
Indication	**Option for augmenting***
Managing agitation and sleep disturbance	Benzodiazepines
Post-psychotic depression or in secondary negative symptoms	Mirtazapine
Weight gain	Topiramate
Agitation and affective symptoms	Lithium
Aggression and hostility	Valproate

* All are level 3/4 evidence

Other biological management options

- Electroconvulsive therapy (ECT)
- Repetitive transcranial magnetic stimulation (rTMS)

Indications for ECT

- Schizophrenia with catatonic features
- Schizophrenia with comorbid depression and/or suicidal ideation where a rapid therapeutic response is needed
- Resistant schizophrenia

Duration of treatment

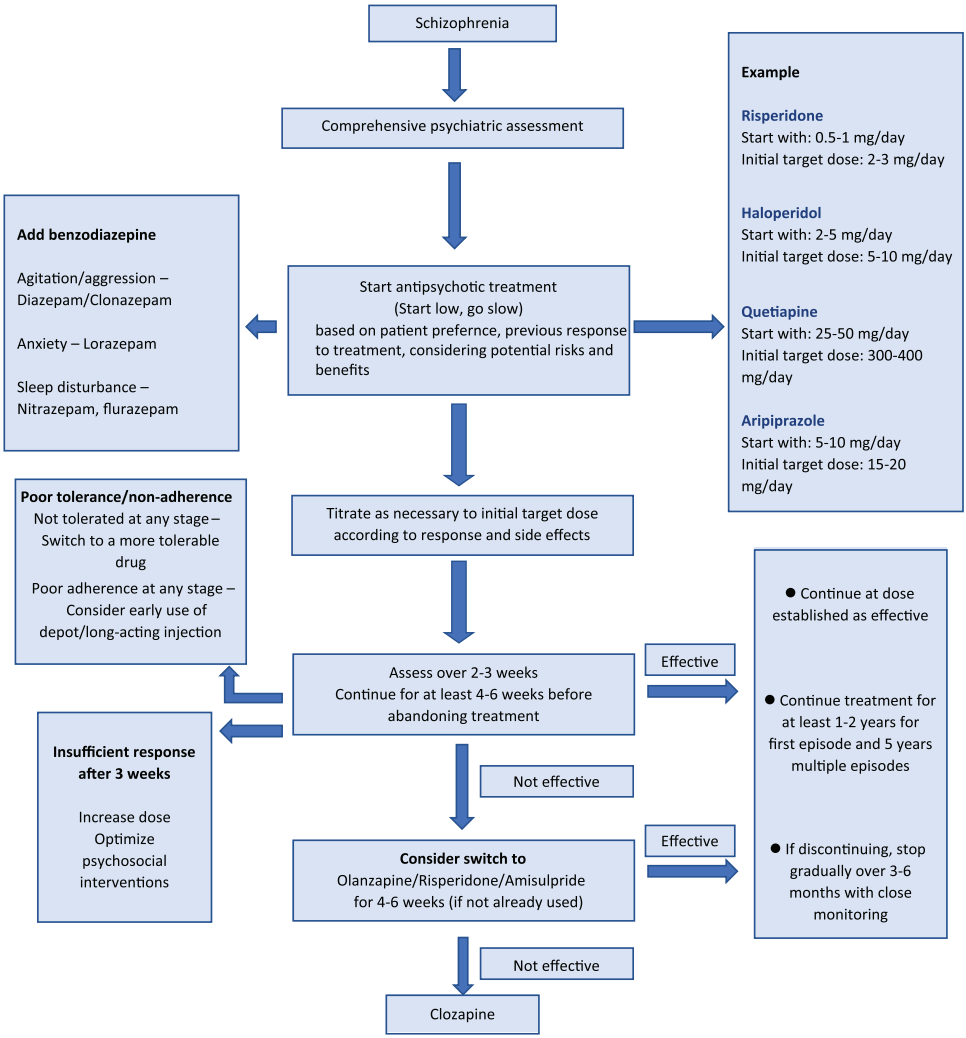
The minimum recommended duration of an effective trial for all antipsychotics is to use in the highest tolerable dose for 6-8 weeks, with the exception of clozapine, where the minimum period of treatment is at least 3-6 months.

Factors to be considered for long term/ lifelong use of antipsychotics

- History of multiple relapses/recurrences while on treatment
- History of relapses when the medications are tapered off
- History of suicidal attempts
- Family history of psychosis with poor outcome
- Comorbid substance dependence

- For patients with first episode of schizophrenia, the duration of maintenance treatment with antipsychotics should be at least 12 months following resolution of symptoms.
- For patients with several episodes or exacerbations should receive maintenance treatment for 5 years or longer after the last episode.
- Some patients may require lifelong treatment.

Treatment algorithm for schizophrenia



Special presentations

Negative symptoms

Flattened affect | Alogia | Avolition | Anhedonia | Social Withdrawal

Management

- Exclude secondary causes like EPS, depression, cognitive impairment, lack of social stimulation
- Choice of antipsychotics for primary negative symptoms

  Amisulpride, Aripiprazole, Clozapine
- Choice of antipsychotics for secondary negative symptoms

  Second Generation Antipsychotics (SGAs)
- Adjunctive antidepressant medication

  Fluoxetine, Sertraline, Mirtazipine
- Other adjunct medication

  Topiramate (especially used to augment clozapine)

Depressive symptoms

- Avoid antidepressants during acute psychosis because of chance of worsening of psychosis
- Choice of antidepressants

  SSRIs: Fluoxetine, Sertraline, Escitalopram

  TCA: Imipramine, Amitriptyline, Nortriptyline

Catatonia

Management

- Rule out extrapyramidal side effects, neuroleptic malignant syndrome, medical causes
- Rule out for any discontinuation of antipsychotics
- Ensure treatment of underlying cause

Step 1

- If patient was not taking antipsychotics and other causes were ruled out, consider SGAs
- Choice of antipsychotics-

  Olanzapine, Risperidone, Aripiprazole, Clozapine

Step 2

- If there is no response in 1-2 days, consider benzodiazepines

  Lorazepam (2-24 mg/day)
- If no response after 1-2 days, consider combining SGA with Lorazepam
- Consider diazepam

Step 3

- If no response, consider ECT

Prognosis

- It is estimated that around three-quarters of people with schizophrenia will experience recurrent relapse and some continued disability. The findings of follow-up studies over periods of 20 to 40 years suggest that there is a moderately good long-term global outcome in over half of people with schizophrenia, with a smaller proportion having extended periods of remission of symptoms without further relapses.
- About 20% of schizophrenia patients achieve complete remission and when full recovery occurs it is within the first two years. Late recovery is also seen in a significant minority of patients.
- Rule of third is – roughly one-third of patients are able to lead normal lives, one-third continue to experience moderate symptoms and one-third remain significantly impaired by their illness for their entire lives. For reason not clear, there is also evidence prognosis is good in developing countries than developed ones.
- While a high proportion respond to initial treatment with antipsychotic medication, around 80% will relapse within 5 years of a treated first episode, which is partly explained by discontinuation of medication.
- Research has suggested that delayed access to mental health services and treatment in early psychosis and schizophrenia – often referred to as the duration of untreated psychosis – is associated with slower or less complete recovery, and increased risk of relapse and poorer outcome in subsequent years.

Comorbid psychiatric conditions

Substance use

General principles for schizophrenia with comorbid substance use

- About 15-65% of patients with schizophrenia has comorbid substance use problem.
- Prevalence of tobacco smoking is highest in schizophrenia among all the mental disorders.
- Smokers with schizophrenia are more likely to have more intense positive symptoms and lower cognitive function, but diminished intensity of extrapyramidal side effects than nonsmoking patients with schizophrenia.
- In the acute phase of illness, treatment should be focused on schizophrenia; substance use can be treated simultaneously.
- Several studies have shown smoking can lower blood levels of some antipsychotics and may also be reinforcing for patients because it improves psychiatric symptoms.
- Smoking increases metabolism of antipsychotics like clozapine, olanzapine and risperidone so higher dosage is required in heavy smokers. When smoking is reduced, dose adjustment is required.
- Higher dosage of antipsychotic is not required to treat schizophrenia with comorbid substance use.
- For substance use other than tobacco, detoxification followed by motivational interviewing, behavioral techniques and other psychosocial interventions maybe considered.

Recommended antipsychotics for comorbid substance use			
	First line	**Second line**	**Best avoided**
Alcohol	Amisulpride	Quetiapine	Chlorpromazine
	Sulpiride	Olanzapine	Clozapine
		Risperidone	(Antipsychotics with high sedating properties)
Cannabis	Any antipsychotic can be used in cannabis use disorder		
Cocaine	Haloperidol	Olanzapine	
		Quetiapine	
		Risperidone	
Tobacco	Nicotine replacement therapy and bupoprion can be used for tobacco use		

*Long acting injectables should be considered in case of non-compliance

Sexual dysfunction

General principles for schizophrenia with sexual dysfunction (SD)

- Schizophrenia patients have higher prevalence of sexual dysfunction than general population
- Antipsychotic treatment may contribute to dysfunction both in men and women
- Routinely ask about any sexual problems in the patients
- First generation antipsychotics and risperidone have higher rates of SD than other antipsychotics
- Aripiprazole, olanzapine, quetiapine exhibits a significantly lower incidence of SD
- APA recommends that patients with schizophrenia whose symptoms have improved with an antipsychotic medication, should continue to be treated with the antipsychotic.

General management

- **Reduction in medication dose**
- **Change in medication may be considered to**

  Aripiprazole, Olanzapine, Quetiapine, Lurasidone, Brexiprazole

Specific Management

- **Assess the type of sexual disorder, whether low desire, erectile dysfunction or orgasmic problems**
- **Low sexual desire**

  Bupropion
- **Erectile dysfunction**

  Sildenafil, Tadalafil, Vardenafil
- **Prolactin induced desire and arousal problem**

  Cabergoline, Bromocriptine, Amantadine
- **Priapism (persistent erection of penis more than 4 hours)**

  It is an emergency side effect, consult with a urologist immediately

Obsessive-compulsive disorder

Schizophrenia patients may present with obsessive compulsive symptoms (OCS) or have comorbid OCD or antipsychotic induced OCS.

First generation antipsychotics (FGAs) are not generally implicated in the development of OCS. Clozapine and rarely, risperidone and olanzapine are frequently associated with emergence of OCS in schizophrenia.

Management of antipsychotic induced obsessive-compulsive disorder

If both psychotic and obsessive symptoms are unresolved

- Change to another antipsychotic with minimal influence on serotonergic systems

  Aripiprazole, Amisulpride, Haloperidol

- Augmentation with SSRI/TCA

  Sertraline, Fluoxetine (or other SSRIs), Clomipramine

- Augmentation with mood stabilizer

  Lamotrigine, Sodium valproate

If psychotic symptoms resolve to a level that it does not impair functioning and obsessive symptoms are present

- Reduction of dose of antipsychotic to minimum sufficient level
- If clozapine is used, reduce dose if possible and/or add Amisulpride or Apripiprazole
- If not possible then try to augment with SSRIs/TCA and or mood stabilizer.

Psychotherapy

Behavioral therapy including exposure and response prevention (ERP) and cognitive behavioral therapy (CBT).

Comorbid medical conditions

Comorbid Illness	General Principles	Recommended Antipsychotics
Hepatic Impairment	● Start with lower dose ● Be cautious with drugs that are extensively metabolized in liver ● Avoid drugs with long half-lives, that are very sedative and very constipating ● Choose a low-risk drug and initially (first six weeks) monitor liver function tests weekly	● First line Amisulpride, Sulpiride ● Second line Haloperidol, Aripiprazole, Quetiapine, Risperidone *No dosage reduction required for amisulpride, sulpiride, aripiprazole. **In mild and moderate hepatic impairment, start at half of the recommend doses for haloperidol, aripiprazole, quetiapine, risperidone; in severe impairment more caution is required.
Renal Impairment	● Avoid drugs that are extensively renally cleared ● Start at a low dose, increase gradually ● Avoid long-acting drugs, drugs with anticholinergic effects, drugs that prolong QTc interval ● Use creatinine clearance and ACR (albumin to creatinine ratio) to decide dose range and titration frequency ● Usual dosing: GFR 10-50 ml/min - use normal dose; GFR <10ml/min – use 1/4 to 1/2 of normal dose	● Haloperidol ● Olanzapine

Comorbid Illness	General Principles	Recommended Antipsychotics
Cardiac Disease	● Perform ECG for all patients at baseline and then yearly. Monitor high risk patients more closely ● Use QTc interval and T wave morphology for making clinical decisions ● If QTc >440 ms (male) and >470 ms (female) but < 500 ms, then reduce drug dose or switch to 1st line drugs ● If QTc > 500 ms or abnormal T wave morphology, then stop the drug and refer to cardiologist ● At usual dose range 1st line drugs have no effect on QT interval	● First line Brexiprazole, Aripiprazole, Lurasidone ● Second line Risperidone, Paliperidone, Olanzapine, Fluphenazine ● Third line Amisulpride, Haloperidol, Quetiapine
Epilepsy	● Patients with epilepsy have increased risk of schizophrenia and experiencing psychotic symptoms ● Pre-ictal, peri-ictal and post-ictal psychotic symptoms are likely to be related with seizure ● Initially optimize anticonvulsants therapy. Postictal psychosis may remit spontaneously or require low doses of antipsychotics. Short term treatment with antipsychotic is recommended for up to 3 months ● Psychotic symptoms occurring independently of seizures or interictal psychosis are likely to require antipsychotics	● First line Risperidone, Aripiprazole, Haloperidol, Trifluoperazine ● Second line Brexiprazole, Lurasidone ● Third line Olanzapine, Quetiapine

Comorbid Illness	General Principles	Recommended Antipsychotics
Parkinson's Disease	● Parkinson's disease can present with visual hallucinations, auditory hallucinations, delusions and features of dementia ● Psychotic symptoms can be the effect of dopaminergic medication rather than part of Parkinson's disease ● Dopamine agonists and anticholinergic drugs are more likely to produce psychotic symptoms than levodopa and catechol-o-methyltransferase inhibitors ● If psychotic symptoms develop, at first try by reducing or stopping anticholinergics and dopamine agonists	● Quetiapine (low dose) ● Clozapine (start at 6.25 mg/day, usual maintenance dose 25-35 mg/day)

Emergency and crisis management

Violent and aggressive behavior

Violent and aggressive behavior can occur in schizophrenia. Risk is elevated when patient has comorbid physical illness, delirium, substance abuse or preexisting personality disorder. Before commencing drug treatment exclude physical illness and delirium, and use de-escalation techniques. De-escalation techniques might involve anticipating violent and aggressive behaviors and preventing them, empathetic verbal and non-verbal communication with the patient, resolving the situation in non-confrontation way, self-management, emotional regulation, etc. Evidence suggests physical intervention such as restraint (using straight/restrain jacket) and seclusion are also effective in managing such cases. Trauma informed room design can provide a sense of calm, safe, dignity, empowerment, and well-being for some patients.

Step 1

- If the schizophrenia patient is on regular antipsychotic-
  Oral treatment with Lorazepam 1-2 mg/Midazolam 7.5-15 mg/Promethazine 50 mg
- If the schizophrenia patient is not taking antipsychotic-
  Oral treatment with Olanzapine 10 mg/Quetiapine 100 mg/Risperidone 1-2 mg/Haloperidol 5mg
- If necessary, repeat after 45-60 minutes
- Considering combining sedatives and antipsychotics
- If it fails or the patient put himself or others at risk, consider IM or IV treatment

Step 2

- IM Lorazepam 2-4 mg/Promethazine 50 mg/Haloperidol 5 mg
- Consider combining drugs if single drug fails-

Haloperidol + Lorazepam/Haloperidol + Promethazine

- Repeat after 30-60 minutes, if necessary

Step 3

- IV Diazepam 10 mg over at least 2 minutes
- Repeat after 10 minutes, if necessary, up to 3 times
- IV treatment may be used over IM when very rapid effect is required

- Monitor temperature, pulse, blood pressure and respiratory rate after commencing treatment, initially every 15 minutes for 1 hour
- ECG is recommended when parenteral antipsychotic therapy is given
- Seek expert advice

Suicidal behavior

Schizophrenia patients have a 10-fold greater risk of suicide than general population.

Recommended steps for suicidal behavior in schizophrenia

- Assessment of the nature of suicidal ideation and behavior is required with a careful search for amenable risk factors
- Enhance psychosocial support with involvement of family members in the treatment
- Ensure medication adherence and follow up
- SGAs are more effective in reducing suicidal risks. The best evidence is for clozapine
- Suicidal behavior when associated with depressive symptoms or major depressive disorders, use SSRI (sertraline, fluoxetine) or imipramine.

Risk factors for suicide

- Previous attempt
- Greater lethality of attempt
- Hopelessness
- Depression
- Commanding hallucinations
- Distressing delusions
- Severe illness as evidenced by early onset
- Frequent relapse and hospitalization
- Receiving high doses of antipsychotics
- Lack of social support
- Comorbid substance abuse
- Age between 20 and 40 years
- Earlier course of illness

Special Population

Pregnancy, postpartum and lactation

General principles for management of schizophrenia during pregnancy, postpartum and lactation

- Women suffering from schizophrenia and unwilling to be pregnant, or are at risk of pregnancy should be assisted in obtaining effective contraception.
- The physiologic alterations of pregnancy may alter the absorption, distribution, metabolism, and elimination of medications and may necessitate adjustments in medication doses.
- There will be better outcome if a multi-disciplinary approach involving obstetrician, partner and care givers is taken.
- If a patient's symptoms are well controlled on a specific medication, it is better to continue that medication if there are no specific contraindications.
- Folate supplementation at 5mg/day is recommended.
- Monitor weight and gestational diabetes throughout pregnancy.
- Usually the first trimester of gestation is associated with risk for teratogenicity. Data suggest that antipsychotic medications have minimal risk in terms of teratogenicity or toxic effects on the fetus.
- There may be more risk of discontinuation symptoms or neurological effects of antipsychotic medications in the newborn when used in the third trimester. So consider the risks and benefits for both mother and infant before tapering off or continuing the antipsychotic medication.
- After delivery, observe for any evidence of neonatal withdrawal, toxicity, extrapyramidal symptoms, sedation or other adverse effects, and ensure that a careful morphological examination is undertaken.

Recommended antipsychotics during pregnancy, postpartum and lactation		
Patient status	**Pregnancy**	**Postpartum and lactation**
Newly diagnosed	Haloperidol	Continue drugs used during pregnancy
	Olanzapine	Chlorpromazine
	Quetiapine	Haloperidol
	Lurasidone	Olanzapine
	Aripiprazole	Quetiapine
		Risperidone
Already on antipsychotics	Continue same drug	Continue drugs used during pregnancy
Incidental/ unplanned pregnancy	Continue same drug	Continue drugs used during pregnancy

*Drug interaction of antipsychotics occur with anesthetic agents

Children and adolescents

General principles for management of schizophrenia in children and adolescents

- Schizophrenia is rare in children but incidence increases rapidly in adolescents.
- A comprehensive multidisciplinary assessment should be ensured.
- Antipsychotic medication should be started after consulting with a psychiatrist.
- Oral medication is preferable to injectable form.
- Electroconvulsive therapy may be used in severely impaired adolescents, if medications are not helpful or cannot be tolerated.

Recommended antipsychotics for children and adolescents

Course of illness	Antipsychotic Drug
Acute episode	Risperidone
	Aripiprazole
	Haloperidol
	Olanzapine
	Quetiapine
	Paliperidone
Maintenance treatment	Continue same drug that responded during acute episode
Treatment resistant schizophrenia	Clozapine in adolescents

Elderly

General principles for management of schizophrenia in the elderly

- Start with low dose and increase slowly and maintain the lowest possible dose for the shortest period. Elderly population usually need half of the adult dose.
- Consider physical and other psychiatric comorbidity as drug interaction is a concern and should be kept in mind while prescribing antipsychotics.
- If possible, avoid drugs which block α1 adrenoceptors, have anticholinergic side effects, are highly sedative, have a long half-life and potent inhibitors of hepatic metabolizing enzymes.
- Late onset schizophrenia needs relatively lower doses of antipsychotics.
- Keep dose of clozapine within 300 mg in the elderly.
- Keep therapy simple; if possible, once daily dosing.

Recommended antipsychotics for the elderly

	First generation antipsychotic	Second generation antipsychotic	Long-acting injectable/ depot antipsychotic
Adult/early onset	Haloperidol	Risperidone	
	Trifluoperazine	Other drugs can be used with caution	
Late onset		Risperidone	Flupentixol decanoate
		Olanzapine	Fluphenazine decanoate
		Quetiapine	
		Aripiprazole	
		Lurasidone	
		Clozapine	

* Long acting injectables should be considered only in case of non-compliance

Psychosocial interventions

Psychosocial interventions are acknowledged as an integral part of management of schizophrenia.

Basic components of psychosocial interventions are

- Assessment of psychosocial factors involving the patient and family
- Promoting a therapeutic alliance with the patient and family
- Information about various aspects of the illness and management
- Focusing on treatment-adherence and healthy lifestyles

Some recommended psychosocial interventions for patients with schizophrenia and their families

- Psychoeducation
- Supportive psychotherapy
- Family intervention
- Social skills training
- Cognitive behavior therapy (CBT)
- Others - Supported employment services
  - Self-management skills
  - Exercise
  - Adherence therapy
- Rehabilitation

Psychoeducation

- Assessing the knowledge of the patient and caregivers about schizophrenia and providing information about etiology, available treatment, their efficacy, likely side effects, duration of use, possible course and long-term outcome.
- Discussing about various symptom dimensions and the diagnosis of schizophrenia, importance of medication and treatment compliance, signs of relapse, problems of substance abuse, marriage and other issues, day to day stress.
- Handling expressed emotions and improving communication.
- Enhancing adaptive coping to deal with persistent/residual symptoms.

Supportive psychotherapy

Supportive psychotherapy is commonly a part of the treatment plan in individuals with schizophrenia who are not receiving other modes of psychotherapy and might be associated with better outcome in coping skills, adherence and relapse.

Common elements of supportive psychotherapy

Reassurance	Praise	Encouragement	Explanation
Clarification	Reframing	Guidance	Suggestion

Family intervention

Family interventions are systematically delivered focusing on the future rather than past events. It is particularly important early in the course of schizophrenia but can also be helpful during any phase of treatment.

Elements of family intervention in schizophrenia
• Education about schizophrenia
• Improving communication
• Lowering expressed emotion
• Expanding social networks
• Adjusting expectations

Social skills training

Social skills training is delivered in a group format and include homework assignments to facilitate skill acquisition. These techniques are aimed to improve typical social behaviors such as making eye contact, smiling at appropriate times, actively listening to others and sustaining conversations.

Techniques used in social skills training
• Role-playing
• Modeling
• Feedback approaches to enhance interpersonal interactions
• Behaviorally oriented exercises in assertiveness
• Appropriate contextual responses
• Verbal and nonverbal communication
• Instruction and practice with social and emotional perceptions

Cognitive behavior therapy (CBT)

CBT for people with psychosis (CBTp) can be used as an adjunct to pharmacotherapy to reduce the distress and disability associated with residual or persistent psychotic symptoms as well as comorbid depression, anxiety and substance abuse.

Two approaches are used. First, to help the patient reduce and cope better with stressors that may be exacerbating the disorder, and cope better with hallucinations. Second, to challenge delusions.

CBTp can be started in any treatment setting, including inpatient settings, although some initial reduction in symptoms may be needed for optimal participation.

Supported employment services

Supported employment differs from other vocational rehabilitation services in providing assistance in searching for and maintaining competitive employment concurrently with job training, embedded job support and mental health treatment.

Self-management skills

Illness self-management training programs are applied to help address many chronic conditions and are designed to improve knowledge about one's illness and management of symptoms.

Aims of self-management skills training program
• Reducing risks of relapse
• Recognizing signs of relapse
• Developing a plan for relapse prevention
• Enhancing coping skills to address persistent symptoms
• Improving overall quality of life, social and occupational functioning

Exercise

Exercise is effective in improving a range of symptoms, quality of life and global functioning in schizophrenia. It is also valuable in general for physical health and for counteracting the weight gain propensity of many antipsychotic drugs.

Adherence therapy (Compliance therapy)

It is a brief intervention using motivational interviewing, which aims to improve outcome by enhancing adherence to treatment use.

Rehabilitation

It is based on a careful assessment of disabilities and deficits and relies on a structured, gradual training. It may be provided in an inpatient unit, a day hospital, or a specialized rehabilitation center. The aim is to return to ordinary work, but those who cannot achieve this are trained for activities such as gardening, crafts, and cooking. This provides a sense of achievement, improve self-esteem and an opportunity for interaction with other people. Payment is an added incentive. Whenever practicable, patients should be encouraged to join the same social groups attended by healthy people and the program need to be culturally molded and adapted to the needs of patients and their families.

Vocational rehabilitation

Vocational rehabilitation aims to improve economic and social participation.

Models of vocational rehabilitation
• Prevocational training Training is provided during a period of preparation before the person seeks competitive employment. • Supported employment Patients are placed in competitive employment with on-the-job support.

Managing side effects of antipsychotics

Side effect	Features	Management
Extrapyramidal side effects (EPSE)	Acute dystonia	● Oral or intramuscular administration of anticholinergic medication (procyclidine, trihexyphenidyl)
	Akathisia	● Dose reduction, or switch to another antipsychotic ● Add a benzodiazepine medication ● Adding an oral beta blocker (propranolol 30–90 mg/day)
	Parkinsonism	● Dose reduction, or switch to another antipsychotic ● Add oral anticholinergic drug (procyclidine, trihexyphenidyl, etc.)
	Tardive dyskinesia (TD)	● Antipsychotic cessation, dose reduction, or switch to another antipsychotic (e.g., olanzapine or aripiprazole) ● Where above fails, consider clozapine ● Use of Tetrabenazine (12.5-150 mg/day) ● Local botulinum toxin injection for focal dyskinesia ● Use of Benzodiazepine (Clonazepam) ● Use of Vitamin E (600-1600unit/day)

Side effect	Features	Management
Anticholinergic effects	Dry mouth	● Drinking small amounts frequently ● Using sugar-free drops or chewing gum ● Dose reduction
	Acute urinary retention	● Transfer of the patient to emergency services ● Dose reduction ● Switching to another antipsychotic
	Constipation	● Dietary supplementation, physical activity ● Pay attention to an adequate fluid intake by the patient ● If constipation persists, use an laxative
Orthostatic hypotension	A drop in blood pressure when changing from lying down or sitting to standing. When severe, orthostatic hypotension can cause syncope, dizziness, or falls	● Supportive measures (e.g., use of support stockings, increased dietary salt and fluid intake) ● Gradual increase in dose ● Decreasing or dividing doses of antipsychotic medication ● Switching to an antipsychotic medication without anti adrenergic effects

Side effect	Features	Management
Sedation		• Lowering of the daily dose • Consolidation of divided doses into one evening dose • Changing to a less sedating antipsychotic medication
Sexual dysfunction		• See page 42
Hypersalivation		• Chew sugarless gum (which stimulates the swallowing reflex) • Only towel on pillow • Use of low-dose or topical anticholinergic medications, such as glycopyrrolate or sublingual ophthalmic atropine 1% drops
Weight gain		• Nutritional management interventions • Exercise and physical activity • Use of metformin • Assess for other contributors to metabolic syndrome

Side effect	Features	Management
Hematological effects		• If severe neutropenia does develop, it is usually reversible if clozapine is discontinued immediately and secondary complications (e.g., sepsis) are given intensive treatment
Dyslipidemia	Certain antipsychotic medications, particularly clozapine and olanzapine, may increase the risk for hyperlipidemia	• Assess for other contributors of metabolic syndrome and ensure that the patient is receiving treatment with a lipid-lowering agent, as clinically indicated
QTc prolongation		• Antipsychotics with a known risk of QTc prolongation are not recommended for use in persons at cardiac risk, if safer medication alternatives are available
Tachycardia		• β-blocking agents can be used for persistent and significant tachycardia • Treatment is not indicated unless the patient is symptomatic or the patient's heart rate is substantially greater than 120 bpm because these medications can contribute to other side effects, such as orthostatic hypotension

Side effect	Features	Management
Glucose dysregulation and diabetes mellitus		• Follow current guidelines for diabetes • Engage in lifestyle interventions to improve diabetes self-management • If possible, switch to another antipsychotic
Hyper-prolactinaemia		• The dose of antipsychotic medication may be reduced • Switch to another antipsychotic with less effect on prolactin (e.g., aripiprazole) • Administration of a dopamine agonist (e.g., cabergoline, bromocriptine, etc.)

Rare but life-threatening side effects of antipsychotics

Side effect	Features	Management
Neuroleptic malignant syndrome (NMS)	An acute disorder characterised by ● muscular rigidity ● hyperthermia ● altered consciousness ● confusion ● autonomic dysfunction (fluctuating blood pressure, tachycardia) following exposure to an antipsychotic ● Raised serum creatinine kinase, SGPT and leukocytosis	● Intensive care management ● Stop antipsychotic treatment ● Measures to reduce body temperature ● Use IV dantrolene (2.5-10 mg/kg/day) ● Use IV lorazepam (4-8 mg/day)
Cardiomyopathy	● Palpitation ● Chest pain ● Syncope ● Sweating ● Dyspnea	● Discontinue drug ● Seek cardiology consultation ● Monitor C-reactive protein, Troponin I, T and ECG
Myocarditis	● Tachycardia ● Fever ● Flu-like symptoms ● Chest pain ● Hypotension ● Fatigue ● Dyspnea ● ECG changes	● Discontinue drug ● Seek cardiology consultation
Seizure		● Anticonvulsant therapy (e.g., valproate) ● Switch to a more suitable drug

Side effect	Features	Management
Hyponatremia	• Confusion • Nausea • Headache • Lethargy • Seizure • Coma	• If mild - fluid restriction • Consider switching to clozapine • Correcting electrolyte disturbance
Heat stroke	• Elevated temperature • Rash • Cramps • Syncope • Delirium • Convulsion • Coma	• Use of cold water, ice packs or water-soaked towels • Support of organ function • Fluid resuscitation and electrolyte replacement • Immediate transfer to a hospital
Drug induced liver injury/ hepatic failure	• Fatigue • Loss of appetite • Distending pain in the liver • Epigastric discomfort • Jaundice • Pale stool • Itching • Altered LFTs	• Stop the drug • Refer to a hospital
Paralytic Ileus	• Abdominal pain • Distension • Elevated serum amylase	• Stop the drug • Bowel rest, intravenous (IV) fluid therapy, nasogastric (NG) decompression • Refer to a hospital
Pneumonia	• Signs of chest infection	• Antibiotics

Section IV

Miscellaneous

Dealing with stigma and misconceptions

Stigma related to mental illness is a widespread issue in Bangladesh and a major impediment towards help-seeking behavior and a high percentage of individuals with mental disorders do not get appropriate treatment. The patients and family members often experience fear, loss, lowered family esteem, shame, secrecy, distrust, anger, inability to cope, hopelessness, helplessness and could be directly blamed for causing the illness.

Stigma leads to discriminations where individuals with mental disorders and their family members may be excluded from interpersonal relationships and public life and legal, economic, social and institutional rights and responsibilities may be denied.

Does schizophrenia run in families?

Schizophrenia is a multifactorial and polygenic disorder. The most important influence is genetic, with about 80% risk of schizophrenia being inherited. However, it is difficult to predict development of schizophrenia in an individual, even if family members have schizophrenia. For instance, if one parent or sibling has schizophrenia, then the individual has a 10-15% higher chance of developing schizophrenia in comparison to the general population. Because of multifactorial and polygenic nature of schizophrenia, it is difficult to predict whether other members will be affected or not.

Can I get pregnant?

Yes. Many women with schizophrenia have healthy pregnancies and babies, but there maybe some risks during pregnancy. Women with schizophrenia are also at risk of developing postpartum psychosis. They should be advised not to stop taking medication without consulting with the doctor as this can lead to withdrawal symptoms, can also cause the symptoms to worsen or return.

Are schizophrenia medicines addictive?

Drugs used in treating schizophrenia are not addictive. They can be discontinued any time. But sudden or premature discontinuation may lead to withdrawal symptoms and relapse. Benzodiazepines, an adjunct medication often used to manage sleep problems can be addictive in some patients if prescribed for longer than 3 weeks.

Do I have to take medicines for the rest of my life?

No. It depends on number of episodes, severity, impact on your life, etc. For first episode, usually 1-2 years after remission, then medicine/s are gradually withdrawn. Majority of the patients experience repeated episodes and they may have to take medicines for a long time in the lowest effective dose.

Why should I continue medicines for a long time?

Schizophrenia is a long-term mental disorder associated with genetically determined brain changes that are often irreversible. There is currently no cure for schizophrenia, though there are medications and other treatments that have proven to be effective in managing certain symptoms, allowing individuals with schizophrenia to achieve quality of life. Long term treatment is necessary to achieve remission, prevent relapses and maintain a productive life.

What preventive measures can be undertaken to prevent relapses?

Following steps can be taken to prevent relapse to some extent

- Staying on medication
- Avoiding stress
- Avoiding addictive drugs like cannabis and alcohol
- Sleeping and eating well
- Not withdrawing from friends and loved ones
- Having a good social support system
- Receiving apprpriate psychosocial interventions

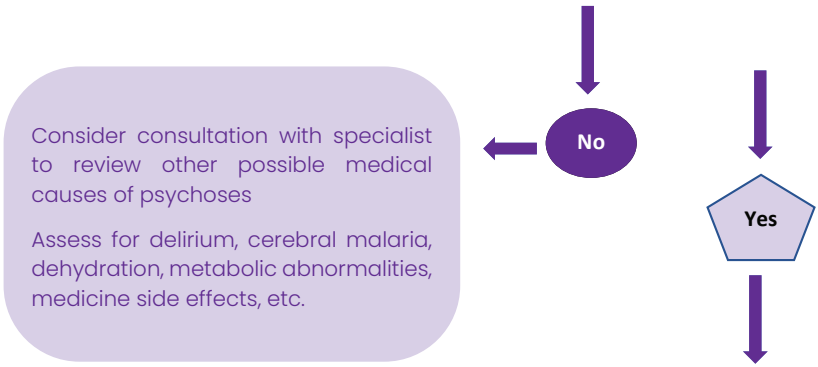
Management in non-specialized settings

Common presentations of psychoses

- Marked behavioral changes, neglecting usual responsibilities related to work, school, domestic or social activities
- Agitated, aggressive behavior
- Delusions (fixed, false beliefs not shared by others in the person's culture)
- Hallucinations (hearing voices, or seeing things that are not there)
- Loss of Insight (lack of realization that one is having mental health problems)

Does the person have at least two of the following?

- Delusions
- Hallucinations
- Disorganized speech and/or behavior, e.g., incoherent/irrelevant speech such as mumbling or laughing to self, strange appearance, signs of self-neglect or appearing unkempt



- Provide psychoeducation to the person and caregivers
- Ensure safety of the person and safety of others
- Promote functioning in daily activities
- Reduce stress and strengthen social supports
- Pharmacological intervention
- Start antipsychotics with a low dose within the therapeutic range and increase slowly to the lowest effective dose, in order to reduce the risk of side-effects.

Recommended antipsychotics for use in management of psychosis in non-specialized settings			
	Dose	Common side effects	Caution
Haloperidol	Start 1.5-3 mg daily Increase as needed (maximum 20 mg daily) orallyor intramuscularly	Sedation Dizziness Blurred vision Dry mouth Urinary retention Constipation	Liver disease Renal disease Cardiac disease
Risperidone	Start 1 mg daily Increase as needed (maximum 10 mg daily) orally	Sedation Dizziness Tachycardia	Cardiac disease
Chlorpromazine	Start 25-50 mg daily Increase as needed (maximum 1000 mg daily) orally	Sedation Dizziness Blurred vision Dry mouth Urinary retention Constipation Tachycardia	Delirium Bone marrow suppression Pheochromo-cytoma

Focus group discussion (FGD) findings

This is a qualitative study done to gather the knowledge, information and experiences regarding schizophrenia in Bangladesh perspective in three different groups (psychiatrists, general practitioners and patients/caregivers' group). The study was done in National Institute of Mental Health (NIMH), Sher-e-Bangla Nagar, Dhaka from 15th October 2021 to 20th December 2021. The participation in the focus group was voluntary, anonymous and confidential.

Key findings

Psychiatrists

Recommended drugs by psychiatrists participating in FGD		
Stage of treatment	**Choice of drug**	**Frequency (%)**
Acute phase	Risperidone	30
	Haloperidol	15
	Olanzapine	15
Maintenance phase	Risperidone	31
	Continuation of drug of acute phase	24
	Aripiprazole	15
Refractory phase	Olanzapine	15
	Long acting Injectable (LAI)	15
	Clozapine	78
Comorbid psychiatric conditions		
Obsessive compulsive disorder	Risperidone	67
	Olanzapine	11
	Trifluoperazine	11
	Chlorpromazine	11
Depression	Olanzapine	41
	Quetiapine	33
	Aripiprazole	17
	Escitalopram	09

	Choice of drug	Frequency (%)
Substance use	Haloperidol	30
	Quetiapine	30
	Risperidone	20
	Olanzapine	10
Sexual dysfunction	Aripiprazole	72
	Quetiapine	28
Comorbid medical conditions		
Heart disease	Haloperidol	37
	Aripiprazole	18
	Risperidone	18
Renal disease	Haloperidol	30
	Risperidone	30
Liver disease	Haloperidol	51
	Olanzapine	25
Diabetes mellitus	Haloperidol	40
	Aripiprazole	40
Special Population		
Children	Risperidone	73
	Aripiprazole	27
Elderly	Quetiapine	35
	Haloperidol	25
	Risperidone	16
	Aripiprazole	16
Pregnant and lactating mother	Lurasidone	50
	Haloperidol	25

Special Presentation	Choice of drug	Frequency (%)
Negative symptoms	Risperidone	37
	Clozapine	18
	Aripiprazole	9
	Lurasidone	9
	Olanzapine	9

General practitioners

It was very disappointing and unexpected that none of the participants representing the general practitioner group got any training focusing on mental illness. They mentioned that social stigma is common in rural people and patients are abused and negatively motivated by quacks and traditional healers at the beginning of the illness and when course of the disease worsens, they visit the physician. The general practitioners also stated that they often refer patients who they find unmanageable and untreatable, and in critical conditions like suicidal behaviors. Answering about the steps minimize the mental health gaps they focused on, and discrimination to mental health in course curriculum of MBBS.

Patients/Caregivers

Risperidone (30%) was the most frequently consumed medication according to the respondent patients (and also their care givers). Tremor (28%), sleep disturbance (17%) and increased salivation (10%) were the commonest side effects of medication reported. 75% of the respondent patients were noncompliant to medication. Advice for oral medication (28%) and medicine with minimum side effects (28%) were the most frequent expectation from drugs followed by effectiveness (19%).

Glossary

Apathy

Diminished emotional expression that includes reductions in the expression of emotions in the face, eye contact, intonation of speech (prosody), and movements of the hand, head, and face that normally give an emotional emphasis to speech

Avolition

Decrease in motivated self-initiated purposeful activities

Alogia

Manifested by diminished speech output

Anhedonia

Decreased ability to experience pleasure from positive stimuli or a degradation in the recollection of pleasure previously experienced

Catatonia

This can occur in the context of several disorders, including neurodevelopmental, psychotic, bipolar, depressive disorders, and other medical conditions (e.g., cerebral folate deficiency, rare autoimmune and paraneoplastic disorders).

When occurs in the context of mental disorders, the clinical picture is dominated by three (or more) of the following symptoms:

- stupor (i.e., no psychomotor activity; not actively relating to environment)
- catalepsy (i.e., passive induction of a posture held against gravity)
- waxy flexibility (i.e., slight, even resistance to positioning by examiner)
- mutism (i.e., no, or very little, verbal response)
- negativism (i.e., opposition or no response to instructions or external stimuli)
- posturing (i.e., spontaneous and active maintenance of a posture against gravity)
- mannerism (i.e., odd, circumstantial caricature of normal actions)
- stereotypy (i.e., repetitive, abnormally frequent, non-goal-directed movements)
- agitation
- grimacing
- echolalia (i.e., mimicking another's speech) and
- echopraxia (i.e., mimicking another's movements)

Negative symptoms

Apathy, avolition, alogia, anhedonia and social withdrawal are called negative symptoms of schizophrenia. Negative symptoms refer to a diminution or absence of normal behaviors related to motivation and interest

Positive symptoms

Delusions, hallucinations, disorganized speech and disorganized behavior are called positive symptoms. Positive symptoms reflect an excess or distortion of normal function.

Relapse

Return of a disease after partial recovery

Remission

A period of time after a previous episode during which no disorder-specific symptoms are present

Social withdrawal

Social withdrawal or asociality refers to the apparent lack of interest in social interactions and may be associated with avolition, but it can also be a manifestation of limited opportunities for social interactions

ICD-11 diagnostic requirements for schizophrenia

Essential (Required) Features:

At least two of the following symptoms must be present (by the individual's report or through observation by the clinician or other informants) most of the time for a period of 1 month or more. At least one of the qualifying symptoms should be from item a) through d) below:

a. Persistent delusions (e.g., grandiose delusions, delusions of reference, persecutory delusions).

b. Persistent hallucinations (most commonly auditory, although they may be in any sensory modality).

c. Disorganized thinking (formal thought disorder) (e.g., tangentiality and loose associations, irrelevant speech, neologisms). When severe, the person's speech may be so incoherent as to be incomprehensible ('word salad').

d. Experiences of influence, passivity or control (i.e., the experience that one's feelings, impulses, actions or thoughts are not generated by oneself, are being placed in one's mind or withdrawn from one's mind by others, or that one's thoughts are being broadcast to others).

e. Negative symptoms such as affective flattening, alogia or paucity of speech, avolition, asociality and anhedonia.

f. Grossly disorganized behavior that impedes goal-directed activity (e.g., behavior that appears bizarre or purposeless, unpredictable or inappropriate emotional responses that interferes with the ability to organize behavior.)

g. Psychomotor disturbances such as catatonic restlessness or agitation, posturing, waxy flexibility, negativism, mutism, or stupor. Note: If the full syndrome of Catatonia is present in the context of Schizophrenia, the diagnosis of Catatonia Associated with Another Mental Disorder should also be assigned.

The symptoms are not a manifestation of another medical condition (e.g., a brain tumor) and are not due to the effects of a substance or medication (e.g., corticosteroids) on the central nervous system, including withdrawal effects (e.g., from alcohol).

DSM-5 diagnostic criteria for schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1 -month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

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Annexures

Oral antipsychotics

Recommended therapeutic dose range of oral antipsychotics available in Bangladesh		
First generation antipsychotics (FGA)	Usual daily dose (mg/day)	Maximum recommended daily dose (mg/day)
Chlorpromazine	200-800	800
Haloperidol	5-20	30*
Trifluoperazine	10-30	30
Second generation antipsychotics (SGA)		
Risperidone	2-8	16
Olanzapine	5-20	30*
Quetiapine	200-800	800
Aripiprazole	10-30	30
Paliperidone	3-12	12
Lurasidone	40-80	160
Clozapine	150-600	900
Amisulpride	50-800	1200
Ziprasidone	40	160
Iloperidone	6	24

*Recommendation from FGD
Patients with first-episode psychosis respond to lower doses (Level 1 evidence)
Higher doses of antipsychotics are controversial, may be used with caution in exceptional circumstances.

Long-acting injectable antipsychotics

Recommended therapeutic dose range of depot/LAI antipsychotics available in Bangladesh		
First generation antipsychotics (FGA)	Usual dose in mg (2-4 weekly)	Maximum dose in mg (2-4 weekly)
Fluphenazine decanoate	25-50	100 mg every 2-4 weeks
Zuclopenthixol decanoate	100-200	600 mg per week
Flupentixol decanoate	20-80	400 mg per week
Second generation antipsychotics (SGA)		
Risperidone depot	25	50 mg every 2 weeks
Paliperidone palmitate	50-150	150 mg per month

Monitoring patients taking antipsychotic medications

	Baseline	6 weeks after starting antipsychotic	12 weeks after starting antipsychotic	Annually thereafter
Weight/BMI	✓	✓	✓	✓
Blood pressure	✓	✓	✓	✓
Fasting blood sugar	✓	✓	✓	✓
Fasting lipid profile	✓	✓	✓	✓
ECG (for patients having personal/family history of cardiovascular disease)	✓	✓	✓	✓
Life style modification advise (including diet and smoking)	✓	✓	✓	✓

A rough guide of relative adverse effects of antipsychotics

Drug	Sedation	Weight gain	Parkinsonism	Akathisia	Hypotension	Anti-Cholinergic	Prolactin elevation
Aripiprazole	-	-	-	+	-	-	-
Chlorpromazine	+++	++	++	+	+++	++	+++
Clozapine	+++	+++	-	-	+++	+++	-
Flupentixol	+	++	++	++	+	++	+++
Fluphenazine	+	+	+++	++	+	+	+++
Haloperidol	+	+	+++	+++	+	+	++
Iloperidone	-	++	+	+	+	-	-
Lurasidone	+	-	+	+	-	-	-
Olanzapine	++	+++	-	-	+	+	+
Paliperidone	+	++	+	+	++	+	+++
Quetiapine	++	++	-	-	++	+	-
Risperidone	+	++	+	+	++	+	+++
Trifluoperazine	+	+	+++	+	+	+	+++
Ziprasidone	+	-	-	+	+	-	+
Zuclopenthixol	++	++	++	++	+	++	+++

*+++ High incidence/severity; ++ Moderate; + Low; - Very low.
Note: The table notes approximate estimates of relative incidence and/or severity, based on clinical experience, manufactures' literature and published research. Other adverse effects not mentioned in this table do occur.