Schizophrenia
### Levels of evidence and grades of recommendation

#### Levels of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td>1**</td>
<td>High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias</td>
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<tr>
<td>1*</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
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<tr>
<td>1</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2**</td>
<td>High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
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<tr>
<td>2*</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
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<tr>
<td>2</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
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#### Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review of RCTs, or RCT rated as 1** and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1*, directly applicable to the target population, and demonstrating overall consistency of results</td>
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<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2**, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1** or 1*</td>
</tr>
<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2*, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2**</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2*</td>
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<tr>
<td>GPP</td>
<td>Recommended best practice based on the clinical experience of the guideline development group (good practice points)</td>
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Schizophrenia
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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive summary of recommendations</td>
<td>1</td>
</tr>
<tr>
<td>1 Introduction</td>
<td>6</td>
</tr>
<tr>
<td>2 Treatment of acute symptoms</td>
<td>11</td>
</tr>
<tr>
<td>3 Maintenance pharmacotherapy</td>
<td>14</td>
</tr>
<tr>
<td>4 Management of treatment-resistant schizophrenia</td>
<td>16</td>
</tr>
<tr>
<td>5 Adjunctive medications</td>
<td>18</td>
</tr>
<tr>
<td>6 Psychosocial Interventions</td>
<td>21</td>
</tr>
<tr>
<td>7 Pregnancy</td>
<td>25</td>
</tr>
<tr>
<td>8 Cost-effectiveness issues</td>
<td>27</td>
</tr>
<tr>
<td>9 Clinical quality improvement</td>
<td>28</td>
</tr>
<tr>
<td>References</td>
<td>29</td>
</tr>
<tr>
<td>Annex I: Initial dosing and clinical titration of antipsychotic drugs</td>
<td>38</td>
</tr>
<tr>
<td>in schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Annex II: Medication algorithm for schizophrenia</td>
<td>39</td>
</tr>
<tr>
<td>Annex III: Monitoring protocol for patients with metabolic syndrome</td>
<td>40</td>
</tr>
<tr>
<td>Annex IV: Comparison of atypical antipsychotics and metabolic</td>
<td>41</td>
</tr>
<tr>
<td>abnormalities</td>
<td></td>
</tr>
<tr>
<td>Annex V: Common side effects of antipsychotic medications</td>
<td>42</td>
</tr>
<tr>
<td>Annex VI</td>
<td>43</td>
</tr>
<tr>
<td>Self-assessment (MCQs)</td>
<td>44</td>
</tr>
<tr>
<td>Workgroup members</td>
<td>46</td>
</tr>
</tbody>
</table>
Schizophrenia is a major psychiatric disorder with a chronic and often disabling clinical course. The early age of onset, impairments in intellectual and psychosocial aspects of the affected individual’s life as well as the associated stigma, places a large burden on affected individuals and their families. According to the latest Singapore burden of disease study, Schizophrenia is the 9th leading cause of disability in Singapore* (2.7% of total disability-adjusted life-years, 2007). Schizophrenia has been incorporated into the national Chronic Disease Management Programme in order to enhance the care for patients with Schizophrenia.

This publication serves to update the first edition of the MOH clinical practice guidelines on Schizophrenia which was published in 2003. I hope that this set of guidelines will be useful to help healthcare professionals in Singapore provide better care for people living with Schizophrenia.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

Executive summary of key recommendations

Details of recommendations can be found in the main text at the pages indicated.

Treatment of acute symptoms

**GPP** The preliminary step in management involves establishing diagnosis and ruling out psychoses that could be secondary to physical morbidity or substance use. The patient’s social supports, functioning and relative risk of self-harm or harm to others must be evaluated for choice of treatment setting (pg 11).

**A** People newly diagnosed with schizophrenia should be offered oral antipsychotic medication (pg 11).

**Grade A, Level 1++**

**GPP** Clinicians must provide information and discuss the benefits and side-effect profile of each drug with the patient (pg 11).

**GPP** The recommended optimal oral dose of antipsychotic is 300-1000 mg chlorpromazine equivalents daily for an adequate duration of 4-6 weeks. Treatment should be started at the lower end of the licensed dosage range and slowly titrated upwards (refer table in Annex II) (pg 12).

**Grade A, Level 1++**

**D** If there is inadequate response by 4-6 weeks or if patient develops intolerable side effects, the medication should be reviewed and another typical or an atypical antipsychotic should be used (refer to algorithm in Annex II) (pg 12).

**Grade D, Level 4**

**A** Oral antipsychotics should be used as first-line treatment for patients with an acute relapse of schizophrenia (pg 13).

**Grade A, Level 1++**
Choice of antipsychotic should take into account the patient’s previous treatment response, side effect experience, co-morbid conditions, compliance history and preference (pg 13).

Maintenance pharmacotherapy

A For maintenance therapy, antipsychotic dose should be reduced gradually to the lowest possible effective dose, which should not be lower than half of the effective dose during the acute phase (pg 14).

   Grade A, Level 1+

B Combination of antipsychotics is not recommended except during transitional periods when patients are being switched from one antipsychotic to another, or when used for clozapine augmentation (refer to Annex II) (pg 14).

   Grade B, Level 2++

C Long-acting depot antipsychotics may be indicated in patients in whom treatment adherence is an issue or when a patient expresses a preference for such treatment (pg 14).

   Grade C, Level 2+

B Long-acting depot antipsychotics should not be used for acute episodes because it may take 3-6 months for the medications to reach a stable steady state (pg 15).

   Grade B, Level 2++

C Patients receiving atypical antipsychotics should be regularly monitored for metabolic side effects (refer to Annex III) (pg 15).

   Grade C, Level 4

Management of treatment-resistant schizophrenia

A Clozapine should be offered to patients whose illness has not responded adequately to treatment despite the sequential use of adequate doses and duration of at least two different antipsychotics (pg 16).

   Grade A, Level 1++
**GPP** For all patients on clozapine, clinicians should have their full blood count monitored weekly for the first 18 weeks and monthly thereafter (pg 16).

**D** Electroconvulsive therapy should be considered for patients who have not responded to an adequate trial of antipsychotics and patients with life threatening symptoms such as catatonia and prominent depressive symptoms (pg 16).

**Grade D, Level 3**

**A** Electroconvulsive therapy should not be prescribed as first line treatment or monotherapy in schizophrenia (pg 17).

**Grade A, Level 1+**

**Adjunctive medications**

**A** Antidepressants should be considered when depressive symptoms emerge during the stable phase of schizophrenia (post-psychotic depression) (pg 18).

**Grade A, Level 1+**

**D** Antidepressants should be used at the same dose as for treatment of major depressive disorder (pg 19).

**Grade D, Level 4**

**A** Anticholinergic agents have been shown to be effective in reducing the severity of antipsychotic-induced extrapyramidal side effects and may be prescribed to patients experiencing these side effects (pg 19).

**Grade A, Level 1+**
Psychosocial interventions

Psychosocial interventions should be tailored to the needs of the patients (pg 21).

Patients and their family members should be educated about the illness, its course, and prognosis as well as the efficacy of the various medications, the anticipated side effects and costs. Family interventions should also incorporate support, problem-solving training and crisis-intervention (pg 21).

Grade A, Level 1+

Early psycho-education and family intervention should be offered to patients with schizophrenia and their families (pg 22).

Grade A, Level 1+

Sheltered, transitional or supported employment should be offered to patients with schizophrenia as part of a psychiatric rehabilitation programme to enhance their vocational skills (pg 22).

Grade B, Level 2++

Cognitive remediation may be considered to improve attention, memory and executive function among people with schizophrenia (pg 23).

Grade A, Level 1+

Cognitive remediation should be provided by occupational therapists within the framework of a psychiatric rehabilitation programme, with a functional goal in mind (pg 23).

Grade A, Level 1+

Psychological therapy, in particular Cognitive Behaviour Therapy (CBT), administered in combination with routine care should be considered for patients with schizophrenia, particularly those with persistent negative and positive symptoms (pg 23).

Grade A, Level 1+

Assertive Community Treatment should be recommended for patients with high rates of hospitalizations as well as for those patients with a high potential for homelessness (pg 24).

Grade A, Level 1+
Pregnancy

**D** Treatment options for schizophrenia patients who are pregnant should be individualised, with consideration of severity of previous episodes, duration of remission since last episode, response to treatment and the woman’s preference after full and informed discussion (pg 25).

*Grade D, Level 4*

**GPP** Schizophrenia patients who are pregnant should be referred for urgent specialist consultation if they have not been seen by a specialist before (pg 25).

*GPP*

**GPP** Abrupt cessation of medications should be avoided in schizophrenia patients who are pregnant as it can increase the risk of relapse, particularly in the early weeks of pregnancy when hormonal changes make the woman more vulnerable (pg 25).

*GPP*

**D** Healthcare providers should provide psychoeducation to women with schizophrenia in the childbearing age-group on the risk considerations in pregnancy and counsel patients on family planning and sexuality issues as is appropriate (pg 26).

*Grade D, Level 4*
1 Introduction

1.1 An overview of schizophrenia

1.1.1 Clinical features

Schizophrenia is a mental illness characterised by a multiplicity of symptoms affecting the fundamental human attributes: cognition, emotion and perception. The early age of onset, varying degree of intellectual and psychosocial impairment and possibility of long-term disability makes schizophrenia one of the most severe and devastating mental illnesses. People with schizophrenia also suffer disproportionately from an increased incidence of general medical illness and increased mortality, especially from suicide, which occurs in up to 10% of patients.\footnote{Introduction}

No single symptom is pathognomonic of schizophrenia. Symptoms of schizophrenia are divided into four categories: positive, negative, disorganized and cognitive symptoms. Various combinations of severity in these four categories are found in patients.

Positive symptoms are those that appear to reflect the presence of mental features that should not normally be present. These include delusions and hallucinations.

Negative symptoms are those that appear to reflect a diminution or loss of normal emotional and psychological function. These include affective flattening (difficulty in expressing emotions), alogia (limited speech with consequent difficulty in maintaining a continuous conversation or saying anything new), avolition (extreme apathy with lack of initiation, drive and energy which result in academic, vocational and social deterioration), anhedonia (lack of pleasure or interest in life) and asociality (social withdrawal and few social contacts). Negative symptoms are less obvious and often persist even after the resolution of positive symptoms.

Cognitive symptoms include impairment in attention, reasoning and judgment, and difficulty in processing information.

Disorganised symptoms refer to disturbances in thinking, speech, behaviour and incongruous affect.
These psychological and behavioural disturbances are associated with a variety of impairments in occupational or social functioning. Although there can be marked deterioration with impairments in multiple domains of functioning (e.g. learning, self-care, working, interpersonal relationships, and living skills), the manifestation of the disorder can vary across persons and within persons over time.

Individuals with schizophrenia may also experience symptoms of other mental disorders, including depression, obsessive and compulsive symptoms, somatic concerns, and other mood or anxiety symptoms.

1.1.2 Aetiology of schizophrenia

Schizophrenia is a complex disorder and arises from a combination of risk factors including genetic vulnerability. Although more than 80% of patients with schizophrenia have parents who do not have the disorder, the risk of having schizophrenia is greater in persons whose parents have the disorder; the lifetime risk is 13% for a child with one parent with schizophrenia and 35-40% for a child with two affected parents and about 50% concordance rate among monozygotic twins.²

The genetic vulnerability arises from a complex combination of multiple genes of small effect. Environmental risk factors are also necessary and some operate early in life.³

1.1.3 Natural history and course

The peak incidence of schizophrenia is at 21 years.⁴ The onset is earlier for men (between ages 15 and 25 years) and later in women (between ages 25 and 35 years). Childhood onset schizophrenia is rare and psychotic symptoms in this age group may not always be indicative of schizophrenia.⁵⁻⁷

The first psychotic episode is often preceded by a prodromal phrase. The prodromal phase involves a change from premorbid functioning and extends up to the time of the onset of frank psychotic symptoms. It may last weeks or even years. During the prodromal phase the person experiences substantial functional impairment and nonspecific symptoms such as sleep disturbance, anxiety, irritability, depressed mood, poor concentration, fatigue, and behavioural deficits such as
deterioration in role functioning and social withdrawal. Perceptual abnormalities and suspiciousness may emerge later in the prodromal phase.8,9

The psychotic phase progresses through an acute phase, a recovery or stabilization phase, and a stable phase. The acute phase refers to the presence of florid psychotic features such as delusions, hallucinations, formal thought disorder, and disorganized thinking. The stabilization (recovery) phase refers to a period after acute treatment. During the stable phase, negative and residual positive symptoms that may be present are relatively consistent in magnitude and usually less severe than in the acute phase. Some patients may be asymptomatic whereas others experience nonpsychotic symptoms such as tension, anxiety, depression, or insomnia.

The longitudinal course of schizophrenia is variable. Complete remission with a full return to a premorbid level of functioning is not common although some individuals are free from further episodes. The outcome following first admission and first diagnosis of schizophrenia with follow-up time of more than 1 year suggests that less than 50% of patients have a good outcome - this is thought to be due to unexplained heterogeneity rather than uniform poor outcome.3 A small proportion (10%-15%) will remain chronically and severely psychotic. Early detection and treatment, however, would lead to a better outcome.10

The management of schizophrenia should take a holistic and multidisciplinary approach. The type and range of intervention is to a large extent specific to the different phases of the illness. In the acute phase of the illness, the patient requires specialised psychiatric care.

Family physicians play an important role in the early detection of those who are psychotic. They are also important in managing patients who are stabilized and require maintenance pharmacotherapy. Most of these stabilised patients are best managed in the community. Further, as the rate of physical illnesses like cardiovascular diseases, obesity and diabetes are higher among patients with schizophrenia as compared to the general population, family physicians would be able to screen and treat these illnesses.11
1.2 **Objectives**

This guideline is an update of an earlier guideline on schizophrenia published by the Ministry of Health, Singapore, in 2003. These guidelines are developed to provide information to clinicians on the evidenced-based treatment for schizophrenia.

1.3 **Scope of this guideline**

This guideline covers the treatment of schizophrenia in general adult population. These guidelines do not cover management of other psychotic disorders like Brief Psychotic Disorders, Schizoaffective Disorders, Bipolar Disorders with psychotic symptoms or Delusional Disorders.

This guideline provides recommendations for the treatment of acute symptoms, maintenance pharmacotherapy, treatment-resistant schizophrenia, adjunctive medication, psychosocial interventions and schizophrenia during pregnancy. Cost-effectiveness issues are also considered in this guideline.

1.4 **Who this guideline is for**

This guideline is intended primarily for all doctors and allied healthcare professionals treating patients with schizophrenia. With the introduction of the Chronic Disease Management Programme (CDMP) in Psychiatry, the care of stable patients with schizophrenia is being transferred to general practitioners in primary care and these guidelines will serve as a useful resource for them.

1.5 **Development process of this guideline**

This guideline was developed by a multidisciplinary workgroup appointed by the Ministry of Health, Singapore. The workgroup consisted of a family practitioner, a family therapist, a healthcare administrator, occupational therapists, a patient advocate, pharmacists, psychiatrists and psychologists.

This guideline was developed by reviewing relevant literature, adapting existing guidelines and by expert clinical consensus with consideration of local practice.
1.6 What’s new in this revised guideline:

- The chapter on treatment of acute symptoms has been enhanced by recommendations for first-episode and relapse of schizophrenia.
- The chapter on maintenance pharmacotherapy has been enhanced with recommendations for monitoring of metabolic side effects and combining antipsychotics.
- The chapter on psychosocial rehabilitation has new recommendations on rehabilitation, cognitive remediation therapy and assertive community treatment.

1.7 Review of guidelines

Evidence-based guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in this guideline. The workgroup advises that this guideline be scheduled for review five years after publication, or when new evidence appears that requires substantive changes to the recommendations made in this guideline.
2 Treatment of acute symptoms

Diagnosis and assessment

**GPP** The preliminary step in management involves establishing diagnosis and ruling out psychoses that could be secondary to physical morbidity or substance use. The patient’s social supports, functioning and relative risk of self-harm or harm to others must be evaluated for choice of treatment setting.

2.1 Antipsychotic medications

**A** People newly diagnosed with schizophrenia should be offered oral antipsychotic medication.

Grade A, Level 1++

Antipsychotic medications, either typical or atypical, have been convincingly shown to be more effective than placebo in the treatment of positive symptoms.\(^{12}\)

The response rates with antipsychotics in studies specifically designed to examine treatment of first-episode schizophrenia are high, ranging from 46% to 96%.\(^{13-14}\) Early treatment with an antipsychotic may be critical in achieving good long-term outcome, in terms of symptom remission, delay of psychotic relapse and prevention of psychosocial deterioration.\(^{13, 15}\)

**GPP** Clinicians must provide information and discuss the benefits and side-effect profile of each drug with the patient.

There are no differences between typical and atypical antipsychotics in terms of their efficacy.\(^{16-18}\) However, there are differences in their side-effects profile (refer to Annex I). Also, atypical antipsychotic usually cost more than typical antipsychotics.
A The recommended optimal oral dose of antipsychotic is 300-1000 mg chlorpromazine equivalents daily for an adequate duration of 4-6 weeks. Treatment should be started at the lower end of the licensed dosage range and slowly titrated upwards (refer table in Annex II).

Grade A, Level 1++

First-episode patients are generally more sensitive to the therapeutic effects and side effects of antipsychotic medication and often require lower doses than patients with chronic schizophrenia. Although there have been no randomised controlled trials among Asian patients, the clinical experience is that local patients may respond to lower doses than the Western subjects.

It can take up to 2 weeks for psychotic symptoms to begin respond to antipsychotic medications and prospective studies have shown that it can take several weeks to achieve remission.

D If there is inadequate response by 4-6 weeks or if patient develops intolerable side effects, the medication should be reviewed and another typical or an atypical antipsychotic should be used (refer to algorithm in Annex II).

Grade D, Level 4

Patients with schizophrenia should receive an adequate trial with whatever antipsychotic medication is chosen by the clinician after consultation with the patient, without casual addition of a second antipsychotic drug for the duration of that trial, which can be terminated because of lack of efficacy or tolerability.

There is lack of efficacy when the patient continues to be symptomatic, especially in terms of positive symptoms in spite of receiving an adequate trial (a trial of a single antipsychotic drug lasting 4-6 weeks with at least 4 weeks on a dose of the medication that is within the therapeutic range). Then the clinician must choose a second antipsychotic medication and complete an adequate trial with the second antipsychotic medication.

However, if the trial fails due to lack of tolerability to the antipsychotic, then the clinician must look closely into the reasons for intolerability and choose the second antipsychotic that has lower propensity to cause that particular side effect.
2.2 Treatment of acute relapse

**A** Oral antipsychotics should be used as first-line treatment for patients with an acute relapse of schizophrenia.

*Grade A, Level 1++*

Systematic reviews and meta-analyses of randomised controlled trials established that antipsychotics were more effective than placebo in the treatment of acute schizophrenic episodes. Antipsychotics are efficacious at inducing remission in about 70% of patients with an acute relapse of schizophrenia.\textsuperscript{23-24}

**GPP** Choice of antipsychotic should take into account the patient’s previous treatment response, side effect experience, co-morbid conditions, compliance history and preference.

A meta-analysis showed that there is no clinically significant difference in efficacy between typical and atypical antipsychotics.\textsuperscript{25} However, there are differences in side effect profiles and cost. Choice of antipsychotic should be guided by consideration of individual patient and treatment-related factors that may influence treatment outcomes. Study has shown that drug regime with poorer tolerability is associated with poorer drug adherence which may ultimately increase the risk of relapse.\textsuperscript{26}
3 Maintenance pharmacotherapy

A For maintenance therapy, antipsychotic dose should be reduced gradually to the lowest possible effective dose, which should not be lower than half of the effective dose during the acute phase.

   Grade A, Level 1+

A meta-analysis of 13 RCTs (N=1395) showed that low-dose therapy may be as effective as standard-dose therapy in terms of efficacy, however, less than half the standard dose is likely to be associated with the increased risk of treatment failure. Compared with the standard-dose treatment, the low-dose therapy did not show any statistically significant difference in overall treatment failure or hospitalization, while the standard dose showed a trend-level (p=0.05) superiority in risk of relapse.27

B Combination of antipsychotics is not recommended except during transitional periods when patients are being switched from one antipsychotic to another, or when used for clozapine augmentation (refer to Annex II) (pg 14).

   Grade B, Level 2++

There is lack of safety data and compelling evidence of superior effectiveness of combining antipsychotics. Most of the data are uncontrolled trials and case reports that describe a mixture of positive and negative findings. Case-control and cohort studies have shown that antipsychotic combined treatment was associated with longer stay in hospital, higher risk of adverse effects and reduced survival.28-30

C Long-acting depot antipsychotics may be indicated in patients in whom treatment adherence is an issue or when a patient expresses a preference for such treatment.

   Grade C, Level 2+

Long-acting depot antipsychotics were developed in the 1960s as an additional method of drug delivery aimed specifically to counter problems of noncompliance.31 Depot preparations could ensure continuous drug delivery and stable plasma concentration over long periods. Patients who refuse their injection or fail to receive it for any other reason can be immediately identified and appropriate action taken.32 Although a systematic review33 has shown no statistically
significant differences between depot and oral antipsychotics in terms of relapse and adverse events, several prospective cohort studies\textsuperscript{34-35} have shown that depot medications were associated with longer time to medication discontinuation.

\textbf{B} Long-acting depot antipsychotics should not be used for acute episodes because it may take 3-6 months for the medications to reach a stable steady state.

\textit{Grade B, Level 2++}

Long-acting depot medications are not usually used for acute episodes because they may take 3-6 months to reach stable steady state.\textsuperscript{36}

\textbf{C} Patients receiving atypical antipsychotics should be regularly monitored for metabolic side effects (refer to Annex III).

\textit{Grade C, Level 4}

The association of weight gain with atypical antipsychotics, possibly over that of typical antipsychotics have been highlighted in several studies\textsuperscript{37-40} A study that systematically reviewed data relating weight changes found that most atypical antipsychotics have been associated with weight increases, with clozapine having the highest risk of weight gain, followed by olanzapine and quetiapine.\textsuperscript{41-43} In another study, olanzapine was associated with significantly greater weight gain when compared to haloperidol.\textsuperscript{44-46}

Associated with weight gain is the concern of metabolic side effects such as dyslipidemia and diabetes. A review of literature showed that low-potency typical antipsychotics (e.g. chlorpromazine, thioridazine) and atypical antipsychotics such as quetiapine, olanzapine and clozapine, were associated with higher risk of metabolic side effects.\textsuperscript{37}
4 Management of treatment-resistant schizophrenia

4.1 Clozapine

Clozapine should be offered to patients whose illness has not responded adequately to treatment despite the sequential use of adequate doses and duration of at least two different antipsychotics.  

Grade A, Level 1++

Meta-analyses of randomised controlled trials support the superiority of clozapine over other antipsychotics for treatment resistant schizophrenia.\textsuperscript{47-48}

GPP For all patients on clozapine, clinicians should have their full blood count monitored weekly for the first 18 weeks and monthly thereafter.

GPP

Agranulocytosis has been reported in 0.8\% of patients receiving clozapine \textsuperscript{49-50} and hence regular monitoring of the full blood count is mandatory. For this reason, clozapine can only be prescribed by registered psychiatrist in Singapore.

4.2 Electroconvulsive therapy (ECT)

Electroconvulsive therapy should be considered for patients who have not responded to an adequate trial of antipsychotics and patients with life threatening symptoms such as catatonia and prominent depressive symptoms.  

Grade D, Level 3

Reports from some studies suggest electroconvulsive therapy combined with antipsychotic medication is more effective than antipsychotic medication alone. Hence patients who have not responded to antipsychotic medications may benefit from the combined use of electroconvulsive therapy and antipsychotic medications.\textsuperscript{51-53}

Clinical experience suggests that patients with prominent catatonic features and mood symptoms benefit from electroconvulsive therapy. Findings from case series and open prospective trials have supported this clinical impression.\textsuperscript{52-53}
Electroconvulsive therapy should not be prescribed as first line treatment or monotherapy in schizophrenia.

Grade A, Level 1+

Electroconvulsive therapy has been reported to be efficacious in the treatment of schizophrenia in case series, uncontrolled and controlled trials. However recent reviews found that there was no significant advantage of electroconvulsive therapy over sham electroconvulsive therapy in the treatment of schizophrenia. Electroconvulsive therapy alone was also found to be less effective compared to antipsychotic medication and electroconvulsive therapy combined with antipsychotic medication.\textsuperscript{51-52}
5 Adjunctive medications

5.1 Mood stabilisers

A substantial proportion of individuals with schizophrenia do not respond adequately to treatment with antipsychotics. Clinicians are thus faced with the challenge of changing to alternative types of medications or augmenting with other drugs such as mood stabilisers.

Several earlier RCTs comparing carbamazepine (either alone or adjunct to antipsychotics) with placebo or antipsychotics were reviewed. In two trials using carbamazepine alone, there was no difference in terms of relapse rates\textsuperscript{54} or improvement in negative symptoms.\textsuperscript{55} In the other studies using adjunctive carbamazepine, there was no difference in terms of improvement of psychotic symptoms.\textsuperscript{56-57}

For lithium, most studies were small and of short duration. There was a meta-analysis of the use of lithium in schizophrenia which concluded that lithium when used as sole treatment is less efficacious than antipsychotics.\textsuperscript{57} Augmentation therapy using lithium was not more efficacious than antipsychotics alone and more subjects left group early as well.\textsuperscript{58-60}

All studies using sodium valproate prescribed it as adjunctive medications\textsuperscript{61-63} There was no evidence of its efficacy in reducing the psychotic symptoms in schizophrenia.

In summary, there is presently insufficient evidence to suggest that lithium, carbamazepine or sodium valproate are effective as adjunctive medications for the treatment of psychotic symptoms in schizophrenia.

5.2 Antidepressants

Antidepressants should be considered when depressive symptoms emerge during the stable phase of schizophrenia (post-psychotic depression).

\textsuperscript{Grade A, Level 1+}
Antidepressants should be used at the same dose as for treatment of major depressive disorder.

**Grade D, Level 4**

A review of antidepressants in patients with schizophrenia or schizoaffective disorder having mood symptoms suggests that antidepressants are likely to be most effective in patients whose acute psychotic episode has been adequately treated with an antipsychotic medication but who subsequently develop a depressive syndrome that meets the criteria for major depressive disorder.

### 5.3 Anticholinergic agents

Anticholinergic agents have been shown to be effective in reducing the severity of antipsychotic-induced extrapyramidal side effects and may be prescribed to patients experiencing these side effects.

**Grade A, Level 1+**

The three types of acute extrapyramidal side effects seen with antipsychotic medications are parkinsonism, akathisia and dystonia. Medication induced parkinsonism is characterised by bradykinesia, tremors and rigidity and is the most common extra-pyramidal side effect seen with antipsychotic medications.

Typical antipsychotics have more propensity to cause these side effects than the atypical antipsychotics. Similarly, younger patients and those with first-episode are more prone to developing extrapyramidal side effects. Other interventions to reduce the severity of extrapyramidal side effects include lowering the dose of the antipsychotic or switching to an atypical antipsychotic. However, anticholinergic agents have limited efficacy in treating akathisia.

The prophylactic use of anticholinergic agents may be considered for those patients who have a higher propensity to developing extrapyramidal side effects e.g. those with prior susceptibility to extrapyramidal side effects or those requiring higher doses of typical antipsychotics.
The effectiveness of and continued need for anticholinergic agents should be assessed in an ongoing fashion. The need for anticholinergic agents should be re-evaluated after the acute phase of treatment is over and whenever the dose of antipsychotic medication is changed.

If the dose of antipsychotic medication is lowered, anticholinergic medication may no longer be necessary and may be withdrawn slowly or the dosage may be reduced.53

As anti-cholinergic use is not without inherent risks including psychiatric effects, it is important to weigh the risks (e.g. euphoria leading to abuse, confusion & hallucinations) and benefits of anticholinergic drug treatment on a regular basis.53
Psychosocial interventions can improve the course of schizophrenia when integrated with psychopharmacologic treatment by providing additional benefits for patients in areas such as relapse prevention, improved coping skills and better social and vocational functioning.

GPP Psychosocial interventions should be tailored to the needs of the patients.

6.1 Psychoeducation / family intervention

Patients and their family members should be educated about the illness, its course, and prognosis as well as the efficacy of the various medications, the anticipated side effects and costs. Family interventions should also incorporate support, problem-solving training and crisis-intervention.

Grade A, Level 1+

Family intervention in the area of psycho-education is an evidence-based practice that has consistently been shown to reduce relapse rates for schizophrenia.23, 70-71

A randomised study showed the efficacy of a basic psychoeducation programme, within a 2-year period, for patients suffering from schizophrenia and their families.72 The programme involved an obligatory-exercise programme where patients and their families were introduced to a series of intervention involving behavioural, assertiveness and communication training and family therapy. The study demonstrated a significant reduction in rehospitalisation rates from 58% to 41% and a shortening of intermittent days spent in hospitalisation from 79 to 39 days.

Another study of multi-family group treatment on an outpatient and inpatient mental health service utilisation involving 97 persons from a randomised sample were investigated. Participants were randomly assigned to standard care or standard care plus family group treatment. Relative to standard care treatment, the family intervention group had reduced hospitalisation during the first year of the treatment at follow-up. These groups also demonstrated a significant increase in outpatient
utilisation. These findings also add to other outcomes such as decreased psychiatric symptoms and caregiver distress.\textsuperscript{73}

The first known controlled trial study on the efficacy of systemic family therapy at the Milan State University.\textsuperscript{74} A longitudinal prospective study was conducted to evaluate the clinical effectiveness of systemic family therapy in the treatment of patients suffering from schizophrenia, as compared to a control case sample composed of patients undergoing routine psychiatric treatment. At the end of 2 years, an improved clinical course and a better pharmacological compliance in the group of patients with systemic family therapy was shown.

A Early psycho-education and family intervention should be offered to patients with schizophrenia and their families.  

Grade A, Level 1+

Advocate for the introduction of family psycho-educational programmes during the early phase of treatment when the patient experiences the first episode.\textsuperscript{75} Group intervention may have more enduring benefits than individual approaches.\textsuperscript{76} However, where families do not attend group intervention, individualised treatment and outreach may be practised instead.

6.2 Psychiatric rehabilitation programme

B Sheltered, transitional or supported employment should be offered to patients with schizophrenia as part of a psychiatric rehabilitation programme to enhance their vocational skills.

Grade B, Level 2++

Studies have shown that sheltered employment, transitional employment and supported employment enhances self esteem, improved subjective well-being and has significant long term functional benefits among the mentally ill population.\textsuperscript{77-80}

Studies have consistently shown that supported employment programmes are associated with increased job placement and tenure rates among patients with schizophrenia.\textsuperscript{81-83}
6.4 **Cognitive remediation**

A Cognitive remediation may be considered to improve attention, memory and executive function among people with schizophrenia.

*Grade A, Level 1+

Systematic reviews and randomised controlled trials have consistently shown that cognitive remediation can produce differential effects on neurocognitive function among patients with schizophrenia.84-88

A Cognitive remediation should be provided by occupational therapists within the framework of a psychiatric rehabilitation programme, with a functional goal in mind.

*Grade A, Level 1+

Studies have shown improvement in occupational and social functioning among patients who have undergone cognitive remediation, in the context of a rehabilitation programme.

6.5 **Psychological intervention**

A Psychological therapy, in particular Cognitive Behaviour Therapy (CBT), administered in combination with routine care should be considered for patients with schizophrenia, particularly those with persistent negative and positive symptoms.

*Grade A, Level 1+

Individual and group psychological therapy can be helpful in addressing the impact of the illness and associated issues in individuals with schizophrenia. Psychological therapy in conjunction with pharmacological intervention can improve global functioning.89 Studies have shown that psychological therapy in combination with routine care can improve overall symptomatology,89-91 and social functioning.92

Cognitive Behavioural Therapy (CBT) in particular, an approach that addresses unhelpful patterns of thinking and behaving, has been shown to be beneficial in reducing the severity of positive and negative symptoms of schizophrenia89, 93-94 and improving overall functioning.91 CBT is also a helpful aspect of early psychosis
CBT and other psychological approaches can help to improve stress management and coping skills, improve insight, and address associated concerns such as depression, anxiety, adjustment difficulties, trauma, interpersonal and social difficulties.

### 6.6 Assertive Community Treatment (ACT)

Assertive Community Treatment should be recommended for patients with high rates of hospitalizations as well as for those patients with a high potential for homelessness.

*Grade A, Level 1+

ACT consists of case management and community based treatment interventions administered by a multi-disciplinary team using a highly integrated approach. This programme is designed to assist patients with schizophrenia avoid relapse and optimise social and occupational functioning. It uses an individually tailored treatment programme that is based on an assessment of each person’s strengths, deficits, and requirements for community living.

ACT has been effective in improving symptom severity\(^\text{95}\) and reducing length of hospitalisations.\(^\text{96-98}\) Compared to those receiving standard community care those receiving ACT were more likely to remain in contact with services, were less likely to be admitted to hospital care and spent less time in hospital.\(^\text{99}\) In terms of clinical and social outcome, significant and robust differences between ACT and standard community care were found on accommodation status, employment, and patient satisfaction.
7 Pregnancy

The care of women with schizophrenia during pregnancy and the postnatal period requires special considerations as treatment decisions are complicated by the presence of the developing fetus, breastfeeding and the timescales imposed by pregnancy and birth, whilst the withdrawal of medications is complicated by risk of relapse, and illness effects on mother and child.

Currently, our understanding of psychotropic drug efficacy and safety in pregnancy is inconclusive, largely from clinical experience, case reports, and birth registry data due to ethical concerns in conducting randomised controlled drug trials in pregnant women.100-102

7.1 Recommendations

**D** Treatment options for schizophrenia patients who are pregnant should be individualised, with consideration of severity of previous episodes, duration of remission since last episode, response to treatment and the woman’s preference after full and informed discussion.103

*Grade D, Level 4*

**GPP** Schizophrenia patients who are pregnant should be referred for urgent specialist consultation if they have not been seen by a specialist before.

**GPP** Abrupt cessation of medications should be avoided in schizophrenia patients who are pregnant as it can increase the risk of relapse, particularly in the early weeks of pregnancy when hormonal changes make the woman more vulnerable.

7.2 Women of childbearing-age with schizophrenia

The care of female patients of childbearing age with schizophrenia is highlighted in these guidelines, given the special needs during pregnancy as detailed above.
Healthcare providers should provide psychoeducation to women with schizophrenia in the childbearing age-group on the risk considerations in pregnancy and counsel patients on family planning and sexuality issues as is appropriate.

Grade D, Level 4

This is important as women with schizophrenia tend to have a higher risk of unplanned pregnancies, and even with withdrawal of drugs with potential teratogenic effects, there remains the risk with early exposure prior to determination of pregnancy.
Schizophrenia is a chronic disease with no definitive cure. Antipsychotic medications, either typical or atypical, are recommended as first-line treatment for patients newly diagnosed with schizophrenia. Both typical and atypical antipsychotic medications have been convincingly shown to be more effective than placebo in the treatment of positive symptoms.105 However, atypical antipsychotic, being newer medications, usually cost more than typical antipsychotics.

A review of RCT-based cost-effectiveness studies for atypical antipsychotics compared to typical antipsychotics conducted between 1985-2003 indicated that the findings from most of the reviewed studies favoured atypical antipsychotics. However, the authors highlighted a number of methodological issues of those studies and suggested there was no clear evidence that atypical antipsychotics generated cost savings or were cost effective in general use among all schizophrenia patients.105

Davis et al conducted a RCT-based cost-effectiveness of typical vs. atypical antipsychotic drugs over a one-year period in the UK, and found that atypical antipsychotics were not cost-effective with additional costs and no gain in quality-adjusted life-years (QALYs) compared with typical antipsychotics. The authors suggested that careful prescribing of typical antipsychotics in routine practice may be cost effective.106

Heeg et al conducted a model-based cost-effectiveness study of typical vs. atypical antipsychotic drugs over a five-year period in the UK. When comparing typical and atypical antipsychotics, the model predicted that atypical antipsychotics resulted in a decrease 5-year costs by £1,633 per patient and in a QALY gain of 0.101. The probabilistic sensitivity analysis in the study suggested that the results were robust. The authors suggested that atypical antipsychotics were cost-effective compared with the typical antipsychotics.107

Overall, the current literature on the cost-effectiveness of atypical vs. typical antipsychotics is mixed, and there is no clear evidence that atypical antipsychotics or typical antipsychotics are more cost-effective.
9 Clinical quality improvement

The following clinical quality improvement parameters, based on the recommendations in this guideline, are proposed:

1) Percentage of schizophrenic patients prescribed antipsychotic medication.

2) Percentage of schizophrenic patients prescribed clozapine, who are unresponsive to adequate trials of two or three antipsychotic medications.

3) Percentage of patients on atypical antipsychotics who are regularly monitored with blood tests for fasting glucose and fasting lipids.
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antipsychotic non-responsive schizophrenia: a double blind, placebo
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### Annex I

**Initial dosing and clinical titration of antipsychotic drugs in schizophrenia**

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Usual Dosage Range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>Acute psychosis: 400-800 Negative symptoms: 50-300</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10-30</td>
<td>72-hour half-life; Efficacy not significantly greater in doses above 10-15 mg/day in RCTs.</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>50-400</td>
<td>Monitor for sedation and postural hypotension</td>
</tr>
<tr>
<td>Clozapine</td>
<td>300-450</td>
<td>Response associated with plasma level &gt;350 ng/ml Compulsory routine hematological monitoring</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>5-20</td>
<td>Monitor for EPS</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>6-12</td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>12-24</td>
<td>Increased risk of extrapyramidal side effects with dosage above 24 mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10-20</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300-800</td>
<td>Safety and benefit of high doses (&gt;800 mg/day) not yet established</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2-6</td>
<td>Increased EPS without improved efficacy above 6 mg/day</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>200-400</td>
<td></td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>5-20</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80-160</td>
<td>Administered with meals; safety and benefits of high doses (&gt;160 mg/day) not yet established</td>
</tr>
</tbody>
</table>
Annex II  Medication algorithm for schizophrenia

1. Medication selection for individual patients is based on physician’s assessment of clinical circumstances, past response/failures on antipsychotics, patient needs, efficacy and side effect profiles of the therapy.
2. Patients require compliance to an adequate trial of antipsychotic (excluding Clozapine) of at least 4-6 weeks at therapeutic doses before being considered as “non-responders” to the medication (Clozapine requires more time, up to 3 months). An adequate augmentation trial of up to 8-10 weeks is required if another antipsychotic is added to Clozapine.
3. Consider Clozapine in those who had failed 2 adequate trials of different antipsychotics (at least 1 should be an atypical).
4. Manage any intolerable side effects accordingly or switch to more suitable alternatives.
5. Consider a depot/long-acting injectable antipsychotic if inadequately compliant.
### Annex III  Monitoring protocol for patients with metabolic syndrome

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (Should be assessed)</th>
<th>After 12-24 weeks</th>
<th>Quarterly</th>
<th>Every Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/Family History</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Waist Circumference</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
### Annex IV Comparison of atypical antipsychotics and metabolic abnormalities

#### Comparison of Atypical Antipsychotics and Metabolic Abnormalities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening Lipid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Aripiprazole*</td>
<td>±</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>±</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paliperidone*</td>
<td>±</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>?</td>
<td>-</td>
<td>?</td>
</tr>
</tbody>
</table>

+ = increase effect  
- = no significant effect  
D = discrepant results  
* = newer drugs with limited long-term data  
?= limited data available for comparison (Taylor and McAskill, 2000)

References consulted:  
Common side effects of antipsychotic medications
1. Sedation
2. Anticholinergic side effects e.g. dry mouth, dry eyes, blurred vision, urinary complaints and constipation
3. Antiadrenergic side effects e.g. postural hypotension, delayed ejaculation
4. Weight gain
5. Transaminitis
6. Cardiovascular side effects include ECG changes e.g. prolonged QTc, cardiac arrhythmias
7. Lowered seizure threshold

Common side effects of typical antipsychotic medications
1. Extrapyramidal side effects e.g. dystonia, akathisia, parkinsonism
2. Tardive dyskinesia
3. Hyperprolactinemia (amenorrhoea, galactorrhoea and breast enlargement in females, and impotence and gynaecomastia in males)
4. Neuroleptic malignant syndrome

Common side effects of specific atypical antipsychotic medications
1. Risperidone: Rhinorhoea, blocked nose and at higher dosages, the side effect profile is similar to typical antipsychotic medications with increased extrapyramidal side effects and hyperprolactinemia
2. Olanzapine: Sedation, weight gain, postural hypotension and anticholinergic side effects
3. Quetiapine: Sedation, postural hypotension, anticholinergic side effects
4. Aripiprazole: Headaches, insomnia and anxiety
5. Ziprasidone: Drowsiness, anxiety and arrhythmias
**Annex VI**

**Indications for hospitalization:**

- Risk of suicide
- Risk of harm to others
- Severe disorganization in behaviour
- Inability of the patient to care for self

**Involuntary admission and treatment**

The Mental Health (Care and Treatment) Act 2008 (MHCTA) has been effective since 1st March 2010 and replaces the old Mental Disorders and Treatment Act. It provides the legal structure for the assessment, admission, detention and treatment of “at risk” individuals who are suspected to be mentally disordered. It provides the legal authority to intervene to protect people with mental disorders and the public from any potential harm arising from the effects of these disorders.

It empowers the police to apprehend and bring an individual who is reported to be of unsound mind and is believed to be dangerous to himself or other persons to a gazetted mental hospital (Woodbridge Hospital) for examination by a medical officer. Compulsory admission is warranted for those deemed to be at risk to themselves or others. These individuals can then be admitted for assessment and treatment for periods stipulated by the law, with reviews and assessments needed to justify further detention of these individuals. (Form I: 72 hours, Form II: 1 month, Form III: 6 months)
After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: http://smj.sma.org.sg/cme/smj/index.html. (the link will only be available once the July 2011 issue of the SMJ becomes available) The answers will be published in the SMJ September 2011 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

**Instruction:** Choose True or False for each statement.

<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
</thead>
</table>

### 1. The following is true of the treatment of schizophrenia in pregnancy and the postpartum:
- **A)** All psychotropic medication must be stopped
- **B)** There is a risk of relapse in the postpartum
- **C)** Care should also be taken to look out for postpartum depressive states
- **D)** Breastfeeding is absolutely contraindicated

### 2. Electroconvulsive therapy
- **A)** is used as a first line therapy for schizophrenia.
- **B)** is more effective than anti-psychotics in the acute treatment of schizophrenia.
- **C)** is effective in the treatment of chronic schizophrenia.
- **D)** may be considered in patients who have not responded to an adequate trial of antipsychotic therapy.
3. Regarding use of anticholinergic agents,
   A) they are effective in treating antipsychotic induced extrapyramidal side effects such as dystonia and parkinsonism  
   B) other interventions to reduce the burden of extrapyramidal side effects include raising the dose of antipsychotics  
   C) the prophylactic use of anticholinergics may be considered for those patients needing higher doses of antipsychotics  
   D) the use of anticholinergics do not carry any inherent risks  

4. Psychological therapy can assist patients with schizophrenia through:
   A) helping to reduce the severity of symptoms  
   B) addressing related issues such as anxiety and depression  
   C) improving coping skills  
   D) eliminating stress and negative thoughts  

5. Antipsychotic medications:
   A) Start showing response by 2 weeks and sometimes take several weeks to achieve remission (T)  
   B) Clinicians should wait for at least for one year before considering switching to another antipsychotic if there is no response to the first antipsychotic medication (F)  
   C) Atypical antipsychotics are superior to typical antipsychotics in terms of efficacy (F)  
   D) Typical antipsychotics have more propensity to cause extra-pyramidal side effects than atypical antipsychotics (T)
Workgroup members

The members of the workgroup, who were appointed in their personal professional capacity, are:

**Chairman**

A/Prof Swapna Verma  
Chief & Senior Consultant  
Department of Early Psychosis Intervention Programme  
Institute of Mental Health

**Members (in alphabetical order)**

<table>
<thead>
<tr>
<th>Ms Chan Lay Lin</th>
<th>Ms Chua Pei Ling, Wendy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Medical Social Worker</td>
<td>Senior Occupational Therapist</td>
</tr>
<tr>
<td>Medical Social Work Department</td>
<td>Institute of Mental Health</td>
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<tr>
<th>Mr Chee Kok Seng</th>
<th>A/Prof Calvin Fones Soon Leng</th>
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<tr>
<td>Principal Clinical Pharmacist</td>
<td>Senior Consultant Psychiatrist</td>
</tr>
<tr>
<td>Community Wellness Centre</td>
<td>Fones Clinic-Psychological Medicine</td>
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<td></td>
<td>Gleneagles Medical Centre</td>
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<thead>
<tr>
<th>Dr Chen Yu, Helen</th>
<th>A/Prof Fung Shuen Sheng, Daniel</th>
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</thead>
<tbody>
<tr>
<td>Head &amp; Senior Consultant Psychiatrist</td>
<td>Vice-Chairman Medical Board (Clinical) &amp; Senior Consultant</td>
</tr>
<tr>
<td>Mental Wellness Service</td>
<td>Department of Child &amp; Adolescent Psychiatry</td>
</tr>
<tr>
<td>KK Women’s &amp; Children’s Hospital</td>
<td>Institute of Mental Health</td>
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<tr>
<th>Dr Chin Swee Aun</th>
<th>Adj A/Prof Sim Kang</th>
</tr>
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<tbody>
<tr>
<td>Deputy Director (Primary Care) Primary and Community Care Division Ministry of Health (till 3 Jan 2011)</td>
<td>Senior Consultant Department of Psychiatry Institute of Mental Health</td>
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<tr>
<th>A/Prof Chong Siow Ann</th>
<th>Ms Khoo Chai Ling</th>
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<tbody>
<tr>
<td>Vice-Chairman Medical Board (Research)</td>
<td>Senior Pharmacist Pharmacy Department</td>
</tr>
<tr>
<td>Institute of Mental Health</td>
<td>Institute of Mental Health</td>
</tr>
</tbody>
</table>
Members (in alphabetical order)

Dr Kwek Seow Khee, Daniel
Senior Consultant
Department of Medicine
Alexandra Hospital

Ms Joycelyn Ling
Senior Psychologist
Department of Early Psychosis Intervention Programme
Institute of Mental Health

Ms Porsche Poh
Executive Director
Silver Ribbon (Singapore) Board Director
World Federation for Mental Health

Ms Tan Bhing Leet
Head of Occupational Therapy Department
Institute of Mental Health

Dr Tan Yong Hui, Colin
Senior Family Physician
Assistant Director Clinical Services
National Healthcare Group Polyclinics

A/Prof Tan Lay Ling
Senior Consultant
Department of Psychological Medicine
Changi General Hospital

A/Prof Tan Chay Hoon
Visiting Consultant
Department of Psychological Medicine
National University Hospital;
Department of Pharmacology
Yong Loo Lin School of Medicine
National University of Singapore

Adj Assistant Prof Tay Woo Kheng
Senior Consultant
Department of Psychological Medicine
Changi General Hospital

Subsidiary editors:

Dr Pwee Keng Ho
Deputy Director (Health Technology Assessment)
Health Services Research & Evaluation Division
Ministry of Health

Mr Raymond Huang
Assistant Manager (Health Technology Assessment)
Health Services Research & Evaluation Division
Ministry of Health
Acknowledgement:

Dr Edwin Chan Shih-Yen  
Head, Epidemiology  
Singapore Clinical Research Institute  
Assoc Professor, Duke-NUS Graduate Medical School, Singapore  
Director, Singapore Branch, Australasian Cochrane Centre;  
Head (Evidence-based Medicine)  
Health Services Research & Evaluation Division  
Ministry of Health
# Levels of evidence and grades of recommendation

## Levels of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1**</td>
<td>High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1*</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2**</td>
<td>High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2*</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
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</table>

## Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review of RCTs, or RCT rated as 1** and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1*, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2**, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1** or 1*</td>
</tr>
<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2*, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2**</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2*</td>
</tr>
<tr>
<td>GPP</td>
<td>Recommended best practice based on the clinical experience of the guideline development group</td>
</tr>
</tbody>
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