# Complete Summary

## GUIDELINE TITLE

Schizophrenia.

## BIBLIOGRAPHIC SOURCE(S)

Singapore Ministry of Health. Schizophrenia. Singapore: Singapore Ministry of Health; 2003 Feb. 40 p. [29 references]

## GUIDELINE STATUS

This is the current release of the guideline.

## ** REGULATORY ALERT **

## FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse**: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 12, 2007, Carbamazepine: The U.S. Food and Drug Administration (FDA) has provided recommendations for screening that should be performed on specific patient populations before starting treatment with carbamazepine.
- September 17, 2007, Haloperidol (Haldol): Johnson and Johnson and the U.S. Food and Drug Administration (FDA) informed healthcare professionals that the WARNINGS section of the prescribing information for haloperidol has been revised to include a new Cardiovascular subsection.
- May 2, 2007, Antidepressant drugs: Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

## COMPLETE SUMMARY CONTENT

## SCOPE

### DISEASE/CONDITION(S)

Schizophrenia

### GUIDELINE CATEGORY

Evaluation
Management
Treatment

### CLINICAL SPECIALTY

Family Practice
Psychiatry
Psychology

### INTENDED USERS

Allied Health Personnel
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

### GUIDELINE OBJECTIVE(S)

- To provide guidance to doctors on the many treatment options available for schizophrenia, based on the best available evidence from the medical literature
- To provide patients with schizophrenia with the best possible care and outcome
- To assist primary health care physicians in clinical decision-making

### TARGET POPULATION

Adults with schizophrenia in Singapore

### INTERVENTIONS AND PRACTICES CONSIDERED

#### Diagnosis and Assessment

1. Assessment of patient for symptoms of schizophrenia, co-morbid psychiatric illness, co-morbid medical condition, or substance abuse
2. Evaluation of patient's social supports, functioning, and relative risk of self-harm or harm to others

**Treatment**

1. Pharmacotherapy
    - First-line antipsychotic medications (trifluoperazine, chlorpromazine, thioridazine, haloperidol, sulpiride)
    - Second-line antipsychotic medications (clozapine, risperidone, olanzapine, quetiapine, amisulpride)
    - Depot antipsychotic medications
    - Maintenance and discontinuation of antipsychotics
    - Adjunctive medications, including anticholinergic agents, benzodiazepines, mood stabilizers (e.g., lithium, carbamazepine, valproate), and antidepressants
    - Monitoring of response to medications and adjustments as necessary
2. Electroconvulsive therapy (ECT)
3. Psychosocial interventions
    - Individual and group psychological therapy
    - Psychoeducation/family intervention
    - Social skills training
    - Vocational training
4. Referral to psychiatrist

### MAJOR OUTCOMES CONSIDERED

- Effectiveness and safety of medications
- Side effects, adverse effects, and costs of treatment
- Rates of relapse, coping skills, social and vocational functioning, and ability to function independently

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

### NUMBER OF SOURCE DOCUMENTS

Not stated

### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

**Levels of Evidence**

**Level Ia**: Evidence obtained from meta-analysis of randomised controlled trials.

**Level Ib**: Evidence obtained from at least one randomised controlled trial.

**Level IIa**: Evidence obtained from at least one well-designed controlled study without randomisation.

**Level IIb**: Evidence obtained from at least one other type of well-designed quasi-experimental study.

**Level III**: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies.

**Level IV**: Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

## METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

### Grades of Recommendations

**Grade A** (evidence levels Ia, Ib): Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

**Grade B** (evidence levels IIa, IIb, III): Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

**Grade C** (evidence level IV): Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.

**Good Practice Points**: Recommended best practice based on the clinical experience of the guideline development group.

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

### METHOD OF GUIDELINE VALIDATION

Not stated

### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The recommendations that follow are those from the guideline's executive summary; detailed recommendations can be found in the original guideline document. Each recommendation is rated based on the level of the evidence and the grades of recommendation. Definitions of the grades of the recommendations (A, B, C, Good Practice Points) and level of the evidence (Level I-Level IV) are presented at the end of the Major Recommendations field.

**A** - Antipsychotic medications are the first-line treatment for psychotic symptoms. (**Grade A, Level Ia**)

**A** - Clozapine is not used as a first-line antipsychotic because of the risk of agranulocytosis. Its use is to be considered only after other antipsychotic medications prove inadequate; it can only be prescribed by a registered psychiatrist, and regular blood monitoring is mandatory. (**Grade A, Level Ia**)

**A** - Most patients respond to a daily antipsychotic dose of 300 to 1,000 chlorpromazine (CPZ) equivalents administered for a minimum of 6 weeks (Dixon, Lehman, & Levine, 1995). Patients with a first episode respond to lower doses than patients with recurrent episodes (McGorry, 1999; Remington, Kapur, & Zipursky, 1998; McEvoy, Hogarty, & Steingard, 1991). (**Grade A, Level Ia**)

**GPP** - Local Asian patients may respond to a lower daily antipsychotic dose. (**GPP**)

**A** - Maintenance dose is generally lower than that used in acute treatment, and the patient should continue with the lowest effective dose of antipsychotic medication. Dosages in excess of 600 CPZ equivalents/day should be avoided unless there are good clinical reasons (e.g., symptom control) for a higher dose (Dixon, Lehman & Levine, 1995). (**Grade A, Level Ia**)

**B** - Patients who have not responded to recommended antipsychotic medications should be considered for electroconvulsive therapy (ECT). (**Grade B, Level III**)

**C** - The prophylactic use of anticholinergic agents should be determined on a case-by-case basis, taking into account risk factors for both extrapyramidal side

effects (EPSE) and anticholinergic side effects as well as the propensity of the antipsychotic medication to cause extrapyramidal side effects. (**Grade C, Level IV**)

**B** - Patients who experience persistent and clinically significant symptoms of anxiety and those with disruptive, dangerous, or assaultive behaviour should receive a trial of adjunctive benzodiazepines (Johns & Thompson, 1995). (**Grade B, Level III**)

**B** - Antidepressants should be considered for persistent depressive symptoms and should be prescribed with an antipsychotic to prevent worsening of psychosis (Black & Andresean, 1999). (**Grade B, Level IIb**)

**B** - Supportive individual and group psychotherapy in combination with medications can reduce relapses and enhance occupational and vocational functioning (Scott & Dixon, 1995). (**Grade B, Level IIb**)

**A** - Cognitive Behavioural Therapy is beneficial in reducing the symptoms (especially the positive symptoms) of schizophrenia (Garety, Fowler, & Kuipers, 2000). (**Grade A, Level Ia**)

**A** - Psychoeducation and family intervention can help reduce relapse rates. (**Grade A, Level Ib**)

**A** - Social skills training improves social adjustment and coping skills, thereby reducing relapse rates (Benton & Schroeder, 1990; Corrigan, 1991). (**Grade A, Level Ib**)

**A** - Vocational training is likely to benefit those who a) see competitive employment as a personal goal, b) have a history of prior competitive employment, c) have a minimal history of psychiatric hospitalization, and d) have been assessed to have good work skills (Lehman, 1995). (**Grade A, Level Ib**)

**Definitions**:

**Grades of Recommendations**

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**Grade C** (evidence level IV): Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.

**Good Practice Points**: Recommended best practice based on the clinical experience of the guideline development group.

### Levels of Evidence

**Level Ia**: Evidence obtained from meta-analysis of randomised controlled trials.

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**Level IIa**: Evidence obtained from at least one well-designed controlled study without randomisation.

**Level IIb**: Evidence obtained from at least one other type of well-designed quasi-experimental study.

**Level III**: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies.

**Level IV**: Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

## CLINICAL ALGORITHM(S)

An algorithm is provided for pharmacological treatment of schizophrenia in the acute phase.

# EVIDENCE SUPPORTING THE RECOMMENDATIONS

## REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

## TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

# BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

## POTENTIAL BENEFITS

### Overall Benefits

- This guideline will provide guidance to doctors on the many treatment options available for schizophrenia and provide patients with the best possible care and outcome.
- Psychosocial interventions can improve the course of schizophrenia when integrated with psychopharmacologic treatment by providing additional benefits for patients in such areas as relapse prevention, improved coping skills, better social and vocational functioning, and ability to function more independently.

### Specific Benefits

- Typical antipsychotic medications have been convincingly shown in well over 100 randomised double-blind studies to be more effective than placebo in the treatment of positive symptoms.
- There is evidence that atypical antipsychotics are more or equally effective in controlling all four categories of symptoms in schizophrenia and are better tolerated than typical antipsychotics.
- Controlled trials have shown that clozapine produces significant improvement in at least 30% of patients who show an inadequate response to two typical antipsychotics of different clinical classes.
- Electroconvulsive therapy (ECT) is effective for schizophrenic patients with affective or catatonic symptoms.
- Randomised trials have demonstrated that a combination of family intervention with antipsychotics reduce 1-year relapse rates from a 40 to 53% range to a 2 to 23% range.
- Studies have shown that, when combined with medications, individual and group psychological therapy reduces relapses and enhances occupational and vocational functioning.
- Cognitive Behavioral Therapy (CBT) has been demonstrated to be beneficial in reducing the symptoms (especially positive symptoms) of schizophrenia.
- Studies show that social skills training improves social adjustment and coping skills, thereby reducing relapse rates.
- Controlled studies have shown that vocational interventions can be effective in helping patients find jobs and remain in competitive employment. Characteristics of patients who are more likely to benefit are those who a) see competitive employment as a personal goal, b) have a history of prior competitive employment, c) have a minimal history of psychiatric hospitalization, and d) have been assessed to have good work skills.

## POTENTIAL HARMS

### Side Effects of Typical Antipsychotics

- Extrapyramidal side effects (e.g., acute dystonia, akathisia, parkinsonism)
- Tardive dyskinesia (involuntary movement disorder) following prolonged use
- Anticholinergic effects (e.g., dry mouth, blurred vision, urinary hesitancy or retention, constipation)
- Anti-adrenergic effects (e.g., postural hypotension, inhibition of ejaculation)
- Sedation
- Lowered seizure threshold
- Cardiovascular effects include electrocardiogram (ECG) changes (e.g., widening of QRS complex, prolonged QT interval), tachycardia, cardiac arrhythmias
- Hyperprolactinaemia (amenorrhoea, galactorrhoea, and breast enlargement in women and impotence and/or gynaecomastia in men)
- Skin and eye effects include allergic and phototoxic skin reactions; long-term use may cause pigmentary changes of skin, and corneal and lens deposits
- Hepatic effects (e.g., minor abnormalities in liver function tests, cholestatic jaundice)
- Neuroleptic malignant syndrome (a rare idiosyncratic and potentially fatal reaction characterized by hyperthermia, muscular rigidity, autonomic

instability, alteration in consciousness level, and elevated serum creatinine phosphokinase)
- Others (e.g., weight gain, nausea)

**Common Side Effects of Atypical Antipsychotics**

*Clozapine*

- Sedation
- Hypersalivation
- Anticholinergic effects
- Weight gain
- Postural hypotension
- Potentially serious agranulocytosis (about 0.34% per annum)
- Potentially serious lowered seizure threshold in doses beyond 600 mg daily

*Olanzapine*

- Weight gain
- Sedation
- Dizziness
- Anticholinergic effects (dry mouth, constipation, retention of urine, blurring of vision)

*Quetiapine*

- Somnolence
- Dizziness
- Postural hypotension
- Anticholinergic effects (dry mouth, constipation, retention of urine, blurring of vision)

*Risperidone*

- Insomnia
- Anxiety
- Agitation
- Hyperprolactinaemia (amenorrhoea, galactorrhoea, sexual dysfunction)

*Amisulpride*

- Insomnia
- Anxiety
- Agitation
- Hyperprolactinaemia (amenorrhoea, galactorrhoea, sexual dysfunction)

**Cautions for Use of Benzodiazepines**

Patients with respiratory difficulties should be treated with caution. All patients should be considered for gradual withdrawal at the earliest opportunity to avoid

an unnecessary risk of dependence, and all patients should be observed for the paradoxical effect of disinhibition.

## QUALIFYING STATEMENTS

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- These guidelines are not intended to serve as standards 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 the guideline document 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, nor should they be construed as including all proper methods of care or excluding 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.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

The following clinical audit parameters, based on recommendations in these guidelines, are proposed:

1. Percentage of schizophrenic patients prescribed antipsychotic medication
2. Percentage of schizophrenic patients prescribed clozapine, who are intolerant or unresponsive to other antipsychotic medications
3. Percentage of schizophrenic patients prescribed clozapine, whose full blood count is regularly monitored

### IMPLEMENTATION TOOLS

Clinical Algorithm
Foreign Language Translations
Patient Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better
Living with Illness

### IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Singapore Ministry of Health. Schizophrenia. Singapore: Singapore Ministry of Health; 2003 Feb. 40 p. [29 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2003 Feb

### GUIDELINE DEVELOPER(S)

Singapore Ministry of Health - National Government Agency [Non-U.S.]

### SOURCE(S) OF FUNDING

Singapore Ministry of Health

### GUIDELINE COMMITTEE

Workgroup on Schizophrenia

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

## GUIDELINE STATUS

This is the current release of the guideline.

## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Singapore Ministry of Health Web site.

Print copies: Available from the Singapore Ministry of Health, College of Medicine Building, Mezzanine Floor 16 College Rd, Singapore 169854.

## AVAILABILITY OF COMPANION DOCUMENTS

None available

## PATIENT RESOURCES

The following is available:

- Schizophrenia. Singapore: Singapore Ministry of Health; 2003. 28 p.

Electronic copies: Available in Portable Document Format (PDF) from the Singapore Ministry of Health Web site.



## NGC STATUS

This summary was completed by ECRI on November 28, 2003. This summary was updated by ECRI on January 18, 2006, following the U.S. Food and Drug Administration advisory on Clozaril (clozapine). This summary was updated by ECRI Institute on October 2, 2007, following the U.S. Food and Drug Administration (FDA) advisory on Haloperidol. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute

on January 10, 2008, following the U.S. Food and Drug Administration advisory on Carbamazepine.

### COPYRIGHT STATEMENT



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