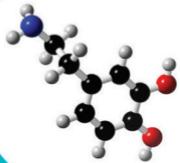


CLINICAL PRACTICE GUIDELINES

May 2009

MOH/P/PAK/185.09(GU)

MANAGEMENT OF SCHIZOPHRENIA IN ADULTS



MINISTRY OF HEALTH
MALAYSIA



MALAYSIAN PSYCHIATRIC
ASSOCIATION



ACADEMY OF MEDICINE
MALAYSIA

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines.

This guideline was issued in 2009 and will be reviewed in 2013 or sooner if new evidence becomes available.

CPG Secretariat

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Electronic version available on the following website:

<http://www.moh.gov.my>

<http://www.acadmed.org.my>

<http://www.psychiatry-malaysia.org>

GUIDELINE DEVELOPMENT AND OBJECTIVES

GUIDELINE DEVELOPMENT

The Development Group for this Clinical Practice Guidelines (CPG) consisted of psychiatrists, a family medicine specialist, public health physicians, a pharmacist, a nursing tutor, an occupational therapist and a social worker. They were from the Ministry of Health and Ministry of Higher Education, Malaysia. During the process of development of this guideline, there was active involvement of the Review Committee.

This CPG was adapted from Schizophrenia Clinical Guideline on Core Interventions in Primary and Secondary Care (National Collaborating Centre for Mental Health/National Institute for Clinical Excellence, Britain, 2003). This CPG was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) prior to adaptation. Evidence was then retrieved from publications year 2003 onwards.

Literature search was carried out at the following electronic databases: PUBMED/MEDLINE, Cochrane Database of Systemic Reviews (CDSR), ISI Web of Knowledge, Health Technology Assessment (HTA), Journal full text via OVID search engine, Database of Abstracts of Reviews of Effectiveness, Psychology and Behavioural Sciences Collection and Cochrane Controlled Trials Register. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. Refer to **Appendix 1** for the terms used to retrieve articles.

Reference was also made to other guidelines on Schizophrenia e.g. Canadian Psychiatric Association 2003, Clinical Practice Guidelines Treatment of Schizophrenia November 2005 (Volume 50, Supplement 1), American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia 2003 (Second Edition), Texas Medication Algorithm Project Procedural Manual (Schizophrenia Treatment Algorithms) and Singapore Clinical Practice Guidelines Schizophrenia 2003.

The clinical questions were divided into four major subgroups and members of the development group were assigned individual topics within these subgroups. The group members met a total of 18 times throughout the development of the guideline. All literature retrieved were appraised by at least two members and presented in the form of evidence tables and discussed during group meetings. All statements and recommendations formulated were agreed upon by both the development group and review committee. Where the evidence was insufficient, the recommendations were

derived by consensus of the development group and review committee. This CPG is based largely on the findings of systematic reviews and meta-analyses in the literature, taking into consideration local practices.

The articles were graded using the modified version of criteria used by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain, while the grading of recommendation in this guideline was modified from the Scottish Intercollegiate Guidelines Network (SIGN).

The draft guideline was posted on the Ministry of Health, Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. This guideline had also been presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council, Ministry of Health, Malaysia for review and approval.

OBJECTIVES

GENERAL OBJECTIVES

To provide evidence-based guidance in the treatment and management of schizophrenia in adults

SPECIFIC OBJECTIVES

- To improve recognition, early intervention and relapse prevention of schizophrenia in health care setting, both in public and private health care facilities
- To promote and enhance evidence-based rehabilitation activities in the management of schizophrenia
- To empower patients and families to be involved in their own care in management of schizophrenia

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

a. Inclusion criteria

- People with a diagnosis of schizophrenia
- People with schizophrenia who are pregnant and lactating – related issues will be addressed in the pharmacological treatment

b. Exclusion criteria

- People with very early-onset (childhood-onset) or very late-onset (age of onset 60 years or more) schizophrenia
- People with schizophrenia with coexisting learning disabilities, substance abuse, or significant physical or sensory difficulties, or those who are homeless

TARGET GROUP/USER

This guideline is applicable all health care professionals who are involved in the management of people with schizophrenia:-

- Psychiatrists
- Family Medicine Specialists
- Emergency Physicians
- Specialists in other specialties
- Medical Officers
- Private General Practitioners
- Medical Social Workers
- Clinical Psychologists
- Pharmacists
- Nurses/Assistant Medical Officers
- Occupational Therapists
- Other Allied Health Professionals

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

CLINICAL AUDIT INDICATORS FOR QUALITY MANAGEMENT

$$\text{Percentage of readmission of people with schizophrenia within six months of last discharge} = \frac{\text{Number of people with schizophrenia for the month readmitted within six months of last discharge}}{\text{Total number of patients admitted in same month}} \times 100\%$$

$$\text{Defaulter rate of people with schizophrenia attending outpatient clinic} = \frac{\text{Number of people with schizophrenia who fail to attend outpatient clinic within one month of appointment date}}{\text{Total number of people with schizophrenia given appointment over same period}} \times 100\%$$

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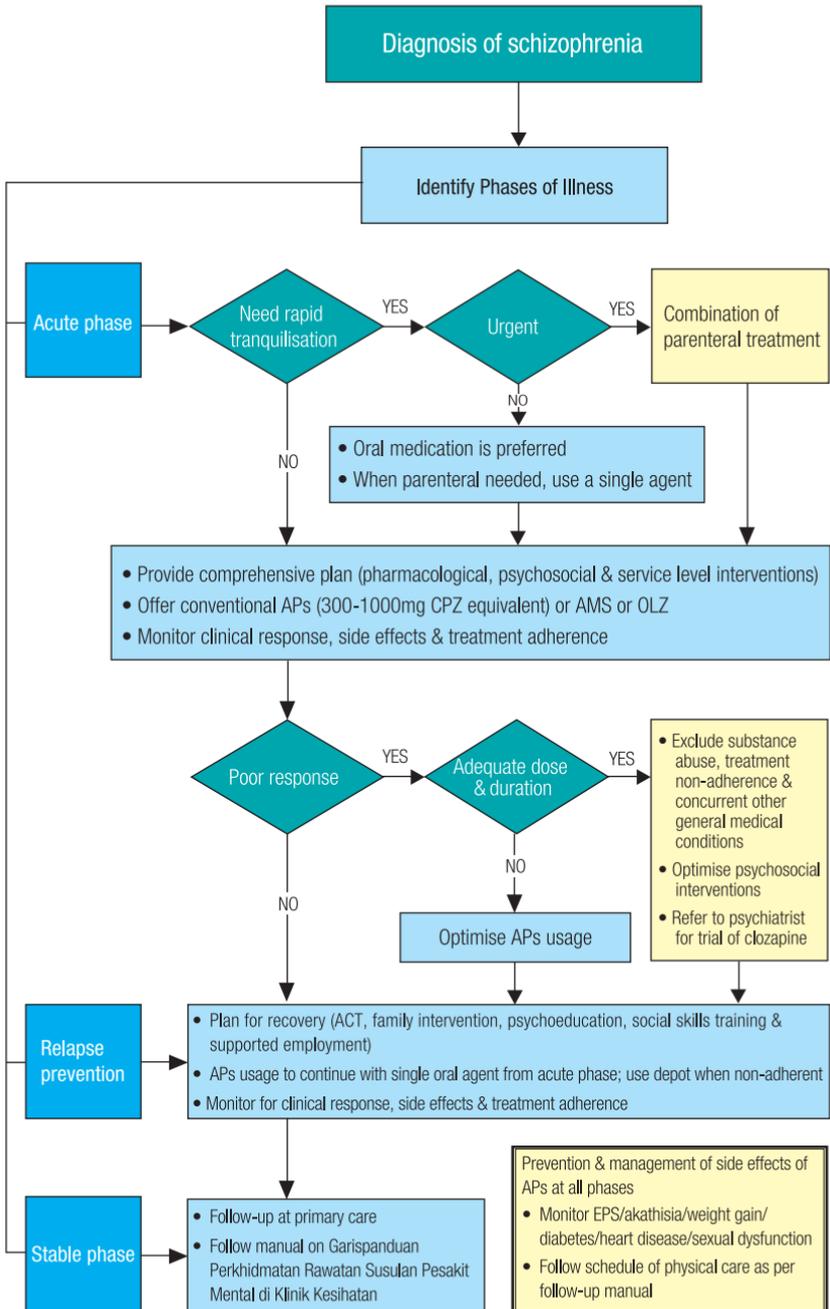
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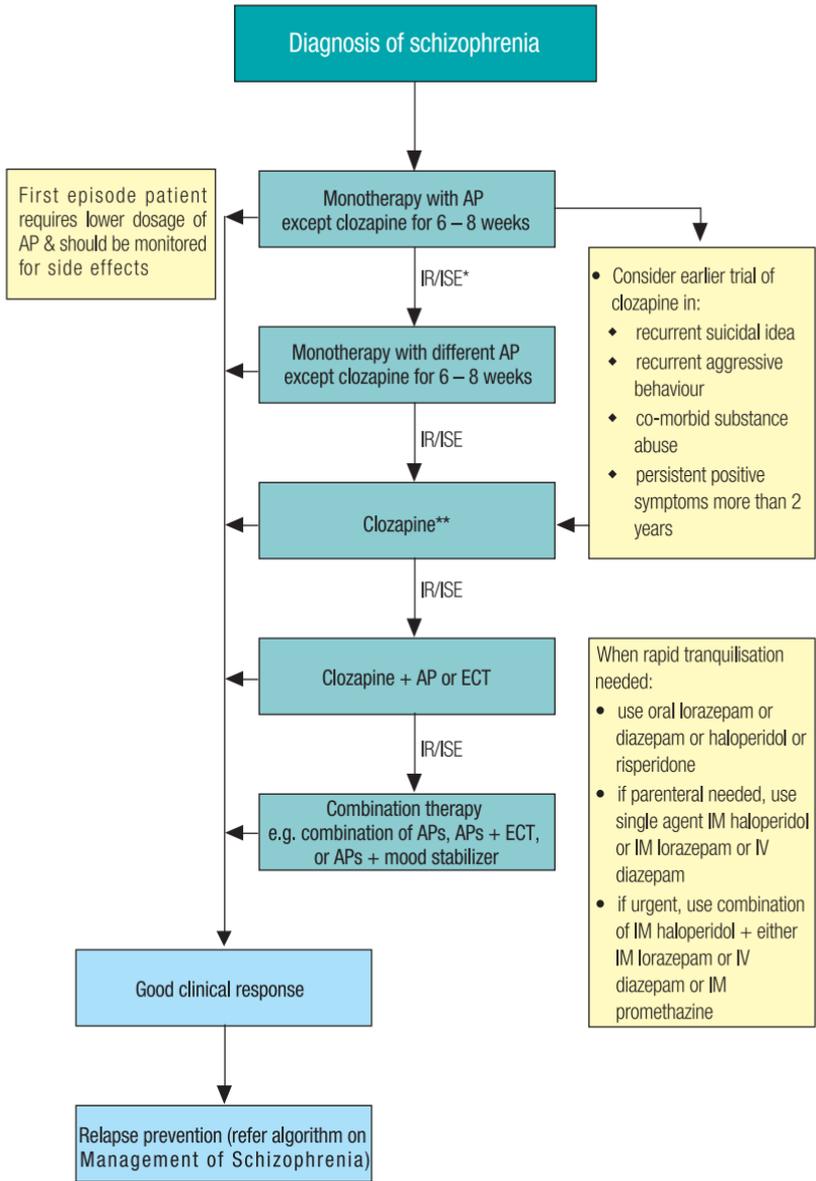
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ALGORITHM FOR MANAGEMENT OF SCHIZOPHRENIA



ALGORITHM FOR MEDICATIONS OF SCHIZOPHRENIA



* IR/ISE = Insufficient response/intolerable side effects

** Refer to psychiatrist for trial of clozapine

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1. EPIDEMIOLOGY, CLINICAL DIAGNOSIS & GENERAL PRINCIPLES OF MANAGEMENT

Schizophrenia is a term used to describe a major psychiatric disorder that alters an individual's perception, thought, affect and behaviour. Malaysia developed its National Mental Health Registry for Schizophrenia in 2003 and 7351 cases had been registered from 2003 to 2005. ^{1, level 8}

In a systematic review (SR) of the incidence of schizophrenia, the median incidence rate was 15.2 per 100,000 (range of 7.7 to 43.0 per 100,000).^{2, level 1} The incidence was noted higher in males, urban and migrant population.

In Malaysia, until the late 1990s, care for people with schizophrenia was mainly centred in the four mental hospitals in the country. In a survey on the implementation of mental health policy in the country, it was found that more than 80% of resources both human, financial and infrastructure were allocated to these four hospitals. ^{3, level 8} Although the first General Hospital psychiatric department was opened in Penang General Hospital in 1959, it was only in the 1990s when decentralization of mental health services really took off with more units in general hospitals being opened all over Malaysia. These units were initially only able to provide basic inpatient and outpatient care due to limited resources. In 2008, there were 28 such units in the country with 22 of them equipped with community-based mental health services.

In early 1980s, there were attempts in providing outpatient care outside the mental hospital and general hospital settings. This was followed by some basic community-based care mainly in terms of home-based follow-up and relapse prevention. In recognition of the limitation of the above, further refinements were made to the hospital-based community psychiatry services. These refinements included acute home care, assertive care and community management of the difficult patients. These aimed to prevent or reduce readmission, by providing more home and community-based treatment; to improve engagement with service users; and to improve clinical, social and occupational outcomes.

Further inroads were made with the implementation of integrated care in primary health care services since 1996. The thrust of primary care in Malaysia is four-fold i.e. mental health promotion, follow-up of stable cases, early detection and treatment and psychosocial rehabilitation. To date, there are 680 health centres providing stable follow-up and early detection and treatment and 27 health centres with psychosocial rehabilitation programmes.

The development of this CPG is essential in Malaysia in view of the rapid changes in psychiatric services, availability of newer medication and the high burden of disease.

1.1 DISEASE BURDEN

The assessment of Years Lived with Disability (YLD) and non fatal burden in Malaysia shows that 21% of the burden was contributed by mental disorders both in men and women. ^{4, level 8}

1.2 CHARACTERISTIC FEATURES

The following characteristics are derived from the findings of Malaysia National Mental Health Registry Report ^{1, level 8}

a. Gender and age

More than 60% schizophrenia cases in Malaysia were males. The peak age of patient's presentation was at the age of 30 in which males developed earlier illness compared to female.

b. Ethnic group

There were 54% Malays, 28% Chinese, 9% Indians and 9% others. This number is consistent with the distribution of ethnic group in Malaysia.

c. Marital status and occupation

Most (80%) were single, divorced, widowed or separated and 70% were unemployed.

d. Body weight

Sixty percent had normal Body Mass Index (BMI<25), 14% overweight (BMI≥25) and 4% obese (BMI>30).

e. Duration of Untreated Psychosis (DUP)

Duration of Untreated Psychosis was described as the time period from onset of the first psychiatric symptom to initiation of antipsychotic treatment. From the cases registered, mean DUP was 28.7 months with a median of 12 months (range 0 to 564 months). Males had a shorter DUP of 23 to 26 months while female had DUP of 30 to 33 months.

f. Family history and co-morbid conditions

A total of 21.6% had family history of mental illness, 20% had some form of co-morbidity, substance abuse being the commonest (80%) of which cannabis was the most common substance abused followed by amphetamine.

g. Medical co-occurring conditions

More than 40% had a co-occurring medical condition; Diabetes Mellitus and Hypertension being the more common ones.

h. Care Setting at First Contact

Slightly more than half of the patients were treated as outpatients but more importantly half of the patients had their first contact as inpatients.

1.3 RISK FACTORS

The risk of developing schizophrenia is higher amongst:

- a. Those with family history of schizophrenia ^{5, level 9}
 - Parents 6%
 - Siblings 9%
 - Children 13%
 - Dizygotic twin 17%
 - Children with two affected parents 46%
 - Monozygotic twin 48%
- b. Those with history of obstetric complications ^{6, level 6}
 - Preeclampsia
 - Extreme prematurity
 - Hypoxia or ischemia during birth
- c. Cannabis abusers ^{7, level 6}
- d. Individual living in higher level of urbanisation (1.40-fold increased risk) ^{8, level 6}
- e. Offspring of older fathers ^{9, level 6}
- f. Unmarried mother ^{6, level 6}
- g. Those with history of childhood central nervous system infection. Viral CNS infections during childhood may have a modest role as a risk factor due to its relative rareness ^{10, level 6}

1.4 CLINICAL DIAGNOSIS

Diagnosis and classification of schizophrenia are not fully discussed in this guideline. However, the diagnosis and classification remain important issues in clinical practice, and the impact of receiving a diagnosis of schizophrenia has considerable social and personal consequences for the individual. Diagnosis is based on DSM IV-TR and ICD-10 (Refer to **Appendix 3**).

The symptoms of schizophrenia can be divided into positive, negative and cognitive symptoms. However, patients may develop their own unique combination of symptoms.

Positive symptoms

The symptoms that appear to reflect the presence of mental features which are not normally present. These include:

- i. Delusions
- ii. Hallucinations
- iii. Disorganised speech/thinking (thought disorder or loosening of associations)
- iv. Grossly disorganised behaviour
- v. Catatonic behaviours
- vi. Other symptoms:
 - Affect inappropriate to the situation or stimuli
 - Unusual motor behaviour (e.g. pacing and rocking)
 - Depersonalisation
 - Derealisation
 - Somatic preoccupations

Negative symptoms

The symptoms that appear to reflect a diminution or loss of normal emotional and psychological function which includes:

- i. Affective flattening
 - the reduction in the range and intensity of emotional expression: facial expression, voice tone, eye contact, and body language
- ii. Alogia or poverty of speech
 - the lessening of speech fluency and productivity, thought to reflect slowing or blocked thoughts, and often manifested as short, empty replies to questions
- iii. Avolition
 - the reduction, difficulty, or inability to initiate and persist in goal-directed behaviour, e.g. no longer interested in going out and meeting with friends, no longer interested in activities that the person used to show enthusiasm for, no longer interested in much of anything, sitting in the house for many hours a day doing nothing
- iv. Negative symptoms are less obvious and often persist even after the resolution of positive symptoms.

Cognitive symptoms

Cognitive symptoms refer to the difficulties with concentration and memory i.e.:

- i. Disorganised thinking
- ii. Slow thinking
- iii. Difficulty understanding
- iv. Poor concentration
- v. Poor memory
- vi. Difficulty expressing thoughts
- vii. Difficulty integrating thoughts, feelings and behaviour

According to the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), the following have been agreed upon as treatment targets for cognitive enhancement in people with schizophrenia ^{11, level 8}

- i. Speed of processing
- ii. Attention/vigilance
- iii. Working memory
- iv. Verbal learning and memory
- v. Reasoning and problem solving
- vi. Visual learning and memory
- vii. Social cognition

1.5 MANAGEMENT OF SCHIZOPHRENIA

The management of schizophrenia may be divided into the following phases:

- Prodromal phase
- Acute phase (refer section 2.3)
- Relapse prevention (refer section 2.4, 2.5, 4 and 5)
- Stable phase (refer section 2.1, 2.2, 2.5, 4 and 5)
- Poor response to treatment (refer section 2.6)

Prodromal phase is characterised by impairments in psychosocial functioning, odd and eccentric behaviour, poor communication and motivation, blunted or flattened affect and neglect of personal hygiene. However, treatment during this phase is still under research and too early to make any recommendations.

This is usually followed by an acute phase when positive symptoms (hallucinations, delusions and behavioural disturbances) of schizophrenia surface. With adequate treatment, the symptoms will disappear in most patients. However, negative symptoms (affective flattening, alogia and avolition) may persist and are similar to that of the prodromal phase.

There are many patterns to the course of illness following the acute phase ranging from excellent adjustment with few relapses to total disability with many relapses. ^{5, level 9} In about 75% of patients, schizophrenia is a chronic disease that causes some degree of disability. In most patients, the deterioration may stop after ten years where they may become stable with sign of improvement.

The management of schizophrenia should be a comprehensive package that includes individually-tailored medication, appropriate psychosocial and service level interventions. The effect size that seems best to reflect clinical significance in the context of evidence-based medicine for binary outcomes is Number Needed to Treat (NNT). ^{12, level 9} Although NNT of 2 or 3 represents a quite high effectiveness of an intervention or test, most NNTs seen in clinical setting with effective interventions will range between 5 and 20. ^{13, level 9} For the purpose of this CPG, Number Needed to Treat (NNT) of less than 10 was agreed to by the Development Group to be considered as effective treatment. The group also found no evidence of effectiveness of traditional and complementary medicine in schizophrenia.

1.6 INTERFACE BETWEEN PRIMARY AND SECONDARY CARE

In Malaysia, Mental Health Services has been provided in most health centres that focus on mental health promotion and providing early detection and treatment, follow-up for the stable mentally-ill and psychosocial rehabilitation. There are two manuals available at the health centre on follow-up of the stable patients and psychosocial rehabilitation i.e. Garispanduan Perkhidmatan Rawatan Susulan Pesakit Mental di Klinik Kesihatan and Garispanduan Pelaksanaan Perkhidmatan Pemulihan Psikososial Bagi Pesakit Mental Di Penjagaan Kesihatan Primer. ^{14, level 9; 15, level 9} People with schizophrenia who present early and for the first time at primary care should be provided with the following:

- Assessment and early treatment
- Early referral to specialist care in the following circumstances:
 - prodromal or attenuated symptoms
 - unclear diagnosis

- plan for psychosocial rehabilitation
- treatment adherence issues
- poor response to treatment
- potential violent behaviour to self or others
- drug-related complications
- co-morbid substance abuse
- special group e.g. pregnancy, paediatric and geriatric age
- Initial treatment and urgent referral in the acutely-ill patient
- Collaboration with hospital-based psychiatric services
- Registration of patients at health clinics and the National Mental Health Registry

When referring patients to specialist mental health services, the following information is useful:

- Past history of treatment and response to medication and side effects
- Adherence to treatment
- Concerns about co-morbid drug and alcohol misuse
- Assessment of risk in all cases and if possible using the Threshold Assessment Grid (TAG) and assessment of needs using the Camberwell Assessment of Needs (CANSAS)
- Assessment of family and social support
- Assessment of physical health

Public primary health care staff should use the standard referral form.

14, level 9

Recommendation

- A local case register at the health centre is recommended as an essential step in monitoring the physical and mental health of people with schizophrenia. **(Grade C)**
- People who develop symptoms of schizophrenia should be diagnosed and treated early. **(Grade C)**
- Health centre staff should regularly monitor the physical health of people with schizophrenia as stipulated in the above-mentioned manual. **(Grade C)**

1.7 CRITERIA FOR HOSPITALISATION

- Risk of harm/neglect to self or others
- Deterioration in psychosocial functioning
- Serious/life-threatening drug reactions

2. PHARMACOLOGICAL TREATMENT

Since the introduction of chlorpromazine in 1952 for the treatment of psychosis, antipsychotic drugs (APs), also known as neuroleptics, have remained to be the cornerstone in the pharmacotherapy of schizophrenia. ^{16, level 1} The APs continue to be used both in the acute and long-term treatment of this condition. The primary mode of action of APs is D2 dopamine receptor blockade. The blockade of D2 receptor more than the therapeutic threshold will cause extrapyramidal side effects (EPS) such as parkinsonism and tardive dyskinesia, and hyperprolactinaemia.

Clozapine challenged the idea of D2 blockade as the main mode of APs action. It was found that clozapine did not work through D2 blockade alone but also involved other receptors e.g. D1, D4, serotonergic, adrenergic and histaminergic receptors. This led to the development of new drugs for the treatment of schizophrenia which were known as atypical APs (AAPs). They were thought to cause less EPS and prolactin elevation but better efficacy as compared to the conventional APs.

APs available in Malaysia, either in oral, intramuscular (IM) or long-acting depot IM preparations are:

Conventional

- Haloperidol
- Chlorpromazine
- Perphenazine
- Sulpiride
- Trifluoperazine
- Fluphenazine
- Zuclopenthixol
- Flupenthixol

Atypical

- Clozapine
- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone
- Aripiprazole
- Paliperidone
- Amisulpride

In the treatment of acute phase of schizophrenia, the recommended optimal oral dose AP is 300–1000 mg chlorpromazine (CPZ) equivalents daily. ^{16, level 1}; ^{17, level 1} CPZ equivalents have been established for conventional APs. For AAPs, it is recommended to use lower end dose ranges. In relapse prevention, standard doses (equivalent to 200–500 mg CPZ) should be used. A table of dose equivalent and dose ranges is available in **Appendix 4**.

- APs are the mainstay of pharmacological treatment in schizophrenia.
- All APs are different in their efficacy and side effects profile.
- APs should be used for at least 6-8 weeks with adequate dosage before switching to other APs.
- Reasons to switch include lack of clinical response, intolerability and drug interaction.
- AAPs are generally associated with a lower risk of EPS than conventional APs such as haloperidol.
- AAPs have a different side effects profile i.e. causing metabolic syndrome (weight gain, dyslipidaemia and glucose intolerance).
- The EPS produced by conventional APs have been shown to be dose-dependent.
- The choice of APs depends on differences in side-effect profiles.
- APs should be used at least 1-2 years for the first episode and for a longer duration in those with chronic schizophrenia.
- If AP is to be withdrawn, it should be done gradually whilst symptoms of potential relapse are monitored for at least two more years.

2.1 COMPARISON BETWEEN CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS

The effectiveness of APs is broadly defined as improvement in psychotic symptoms, quality of life, discontinuation rate or relapse prevention. NICE recommended the use of some AAPs as treatment of choice in newly-diagnosed schizophrenia. ^{16, level 1} It is a good clinical practice that the choice of using APs should be based on the agreement between patients and doctors weighing the benefits of medications and their side-effect profiles. In a meta-analysis by Davis et. al., the effect sizes were NNT=4 for clozapine, NNT=6 for amisulpride, NNT=8 for risperidone and NNT=9 for olanzapine. ^{18, level 1}

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, using discontinuation rates as a measure of effectiveness, demonstrated olanzapine to be superior compared to perphenazine, risperidone, quetiapine and ziprasidone (discontinuation rates of olanzapine at 64%, perphenazine 75%, risperidone 74%, quetiapine 82% and ziprasidone 79%; NNT=8 to 9). ^{19, level 2} However, more patients (9%) stopped taking olanzapine due to significant weight gain, glucose impairment and dyslipidaemia ($p<0.001$) and more patients (8%) discontinued perphenazine as a result of EPS ($p=0.002$).

There was no difference in quality of life improvement between conventional and atypical AP over one year when APs were switched either due to efficacy or side effects (estimated difference -1.7, 95% CI -4.5 to 1.1).^{20, level 2}
^{21, level 2} Switching to conventional APs from AAPs resulted in lower cost of treatment. The probability for conventional APs being more cost-effective was between 0.54 and 0.81.

A recent meta-analysis involving 150 randomised clinical trials (RCTs) demonstrated superiority with regards to negative symptoms, positive symptoms and overall symptoms improvement for three AAPs compared to conventional APs (amisulpride NNT=6, clozapine NNT=4 and olanzapine NNT=6).^{22, level 1} However, aripiprazole, quetiapine, sertindole, ziprasidone and zotepine were no more effective than conventional APs in positive and negative symptoms. Quality of life was better for amisulpride, clozapine and sertindole. Relapse prevention was only slightly better for olanzapine (NNT=17), risperidone (NNT=11) and sertindole (NNT=14). Amisulpride, aripiprazole, quetiapine and clozapine showed no significant difference in preventing relapse. With the exception of aripiprazole and ziprasidone, AAPs induce more weight gain than haloperidol but not more than low potency conventional APs.

Recommendation

- Choice of APs should be based on the agreement between people with schizophrenia and clinician taking into account the relative benefits of the drugs and their side-effect profile. **(Grade A)**
- People with schizophrenia who respond well to conventional APs without side effects should not be changed to AAPs. **(Grade A)**
- Oral AAPs (amisulpride or olanzapine) should be considered as treatment options. **(Grade A)**
- When there is a need to change APs due to EPS or lack of efficacy, switching to AAPs confer no advantage in term of quality of life or cost. **(Grade A)**
- People with schizophrenia who are taking AAPs should be monitored closely for emergence of metabolic syndrome. **(Grade A)**

2.2 EFFECTIVE DRUG TREATMENT FOR PERSISTENT NEGATIVE SYMPTOMS, AGGRESSIVE SYMPTOMS, COGNITIVE SYMPTOMS, MOOD SYMPTOMS AND SUICIDAL BEHAVIOUR

Symptoms of schizophrenia include positive, negative, mood, behavioural and cognitive symptoms. Most RCTs address the general symptoms of schizophrenia by using the reduction of overall scores in symptom rating scale e.g. Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). It is assumed that the effects of APs are mainly results of reduction in positive symptom scores. It is also suggested that the effects of APs on negative symptoms are variable.

Clinicians should first assess and treat any causes of secondary negative symptoms e.g. depression, over-sedation, EPS, anxiety or paranoid delusion.

a. Negative symptoms

Combination of AP and antidepressant was more effective than AP treatment alone in the treatment of persistent negative symptoms of schizophrenia (NNT 3, 95% CI 3 to 34) but this finding was based on two small RCTs. ^{23, level 1}

Olanzapine, quetiapine and risperidone had significantly reduced negative symptoms in people with schizophrenia with prominent negative symptoms ($p < 0.001$). ^{24, level 2; 25, level 3} In another study, flupenthixol proved to be non-inferior to risperidone in the treatment of patient with prominent negative symptoms ($LS_{\text{means}} = 1.60$, 95% CI -1.63 to 4.83). ^{26, level 2}

Olanzapine was associated with significant improvement in primary negative symptom compared to haloperidol plus benztropine combination ($p < 0.05$). ^{27, level 3}

b. Aggression symptoms

Clozapine was superior to both haloperidol ($p < 0.001$) and olanzapine ($p < 0.001$), and olanzapine is superior to haloperidol ($p < 0.001$) in treating aggression. ^{28, level 2}

c. Cognitive symptoms

Cognitive symptoms improvement was noted with conventional AP. ^{29, level 1}

In the CATIE study, there was improvement in neurocognition after 2 months of treatment (olanzapine $p < 0.002$, perphenazine $p < 0.001$, quetiapine $p < 0.001$, risperidone $p < 0.001$, ziprasidone $p < 0.06$) but no differences were noted between the treatment groups. ^{30, level 2}

d. Mood symptoms

In those with depression, amisulpride, clozapine, olanzapine, aripiprazole and quetiapine, were significantly better (NNT = 3 to 18) than conventional APs, whereas risperidone was not. ^{22, level 1}

e. Suicidal behaviour

In a large RCT comparing the risk for suicidal behaviour in schizophrenia, clozapine was found to be superior in reducing significant suicide attempts (NNH=25), had less hospitalisation to prevent suicide (NNH=20) and less worsening of suicidal symptoms (NNH=12) compared to olanzapine. ^{31, level 1}

Recommendation

- Combining APs and antidepressant can be used in treatment of persistent negative symptoms. **(Grade A)**
- Olanzapine, quetiapine and risperidone are superior to conventional APs in the treatment of persistent negative symptoms. **(Grade B)**
- All APs are equally effective in treatment of persistent cognitive symptoms. **(Grade A)**
- Clozapine is superior in the treatment of persistent aggression. **(Grade A)**
- Clozapine is indicated in the treatment of persistent suicidal thoughts or behaviours. **(Grade A)**

2.3 RAPID TRANQUILISATION

Behavioural disturbances are commonly seen during the acute psychotic episode. It can be potentially harmful to patients, carers and staff. Patients with such situation need to be given immediate and urgent attention to prevent further untoward events. NICE has recommended that training on the proper management of violent behaviour of patient should be provided. ^{16, level 1}

- Steps should be taken to minimise the environmental and social risk factors that increase violence during an acute episode when patient is brought to the hospital. These include overcrowding, lack of privacy, lack of activities, long waiting time, poor communication, and poor clinical leadership.
- When patient is to be secluded and rapid tranquilisation is needed, monitoring must be done with more diligence.

The rapid tranquilisation frequently used in Malaysia include intramuscular (IM) injection of APs (e.g. haloperidol, olanzapine, ziprasidone and zuclopenthixol acetate/clopixol acuphase®) and benzodiazepine (e.g. diazepam and midazolam). Other preparations available are orodispersible olanzapine (zydis ®) and risperidone oral solution.

Medications used in rapid tranquilisation include oral and parenteral preparations. ^{16, level 1} If patient fails to take oral medication, parenteral preparations may prove to be mandatory. The use of IM chlorpromazine is associated with hypotension and cardiotoxicity, and therefore not recommended.

According to NICE, violent behaviour can be managed without the prescription of unusually high doses of APs. ^{16, level 1} The maximum dose recommended in **Appendix 4** should be strictly followed. Oral medication should be offered before parenteral medication. The IM route is the preferred choice when parenteral treatment is indicated.

- Rapid tranquillisation is the pharmacological management of the acute behavioural disturbances in schizophrenia i.e. agitation, aggression and potentially violent behaviour.
- The aim of rapid tranquillisation is to achieve sedation in order to minimise the risk of harm to the patients and others.
- When using parenteral preparation for rapid tranquilisation, emergency resuscitation equipments and drugs should be readily available. There should be close monitoring of vital signs (blood pressure, pulse rate, respiratory rate and temperature).
- While the patient is being restrained and sedated, precautions should be taken to avoid over-sedation and failure to detect an underlying medical condition.

Combination of IM haloperidol and IM lorazepam may produce a faster response than IM haloperidol alone. ^{16, level 1} Recent evidences showed the following:

- a. IM haloperidol plus promethazine had faster onset of action when compared to midazolam or haloperidol alone (NNT=5, 95% CI 3 to 8). ^{32, level 1} This combination also had less side effects compared to haloperidol alone (NNH=15, 95% CI 14 to 40)

- b. IM olanzapine had the same onset of rapid action as the combination of haloperidol plus promethazine (RR=0.74, 95% CI 0.38 to 1.41) but required additional drugs within four hours (NNT=5, 95% CI 4 to 8) and more re-assessment by the doctor (NNT=6, 95% CI 5 to 12). ^{33, level 2} However, compared to lorazepam, it had an advantage of requiring less re-injection within 24 hours (NNT=10, 95% CI 6 to 59) and less side effects.

- c. IM zuclopenthixol acetate was found to be no more sedating after two hours when compared to IM haloperidol alone (RR=0.6, 95% CI 0.27 to 1.34) but had reduced need for additional benzodiazepine use (NNT=2, 95% CI 2 to 4) and needed lesser injection over seven days (NNT=4, 95% CI 3 to 14). ^{34, level 1} There was no differences in side effects between them (RR=0.74, 95% CI 0.43 to 1.27).

- d. Oral risperidone was equally effective when compared to IM haloperidol plus lorazepam. ^{35, level 2}

Recommendation

- Proper training on therapeutic management of violent behaviours should be given to health care providers. This includes appropriate skills to be acquired on de-escalation techniques, restraints, seclusion procedures and pharmacological interventions. **(Grade A)**
- Violent behaviour can be adequately controlled with standard doses of APs using minimum effective dose. **(Grade A)**
- Oral medication should be offered before parenteral medication. **(Grade B)**
- IM route for APs is the preferred route when parenteral treatment is chosen. **(Grade C)**
- IM preparations that can be used for rapid tranquillisation are lorazepam, midazolam, haloperidol, olanzapine, ziprasidone and zuclopenthixol acetate. Wherever possible, a single agent is preferred. **(Grade A)**
- When rapid tranquillisation is urgently needed, a combination of IM haloperidol plus lorazepam or IM haloperidol plus promethazine should be considered. **(Grade B)**
- IV diazepam should be used for management of violent behaviour rather than IM diazepam due to its erratic absorption. **(Grade C)**

2.4 RELAPSE PREVENTION

Preventing relapse is a key quality indicator in the management of people with schizophrenia in Malaysia.

Relapse is defined as hospitalisation for psychopathology or a 20% increase in the PANSS score, increased level of care; self-injury, suicide or homicidal ideation or violent behaviour; or a Clinical Global Impression (CGI) rating of above 6.

Certain oral AAPs have been recommended as treatment options for individuals on conventional APs who are experiencing relapse. ^{16, level 1} Use of depot preparations may be considered when treatment adherence issue arises. APs treatment should be initiated as part of a comprehensive package including psychosocial and service level intervention. Monitoring of symptoms and side effects is important when APs are changed. Wherever possible, monotherapy should be used. Conventional APs should not be combined with AAPs except during the short change over period.

A meta-analysis of 14 RCTs comparing AAP with conventional AP in relapse prevention for six months or more found the following ^{22, level 1}:

- olanzapine (NNT=17, 95% CI 8 to 100)
- risperidone (NNT=11, 95% CI 7 to 33)
- sertindole (NNT=14, 95% CI 8 to 50)
- amisulpride, aripiprazole and clozapine showed no significant difference
- quetiapine showed no difference compared with haloperidol in a large unpublished study
- no studies were available for zotepine and ziprasidone

The above meta-analysis included only studies using haloperidol or low-potency conventional APs as comparators to address the important distinction of high-potency versus low-potency conventional APs. ^{22, level 1}

Recommendation

- AP is the mainstay of treatment for relapse prevention. **(Grade A)**
- Amongst all APs, there is no difference in efficacy in relapse prevention. **(Grade A)**
- Depot preparations may be considered when treatment adherence issue arises. **(Grade A)**
- APs treatment should be part of an overall management plan that includes psychosocial and service level intervention. **(Grade A)**
- Monotherapy should be used wherever possible. **(Grade A)**
- Conventional APs should not be combined with AAPs except during the short switching period. **(Grade A)**

2.5 DEPOT ANTIPSYCHOTIC TREATMENT

Depot APs refer to long-acting injectable preparations of APs which are used in the long-term pharmacological treatment of schizophrenia.

Depot APs available in Malaysia are:

- Fluphenazine decanoate
- Flupenthixol decanoate
- Zuclopenthixol decanoate
- Risperidone

Depot APs may confer an advantage over conventional oral APs by improving adherence to drug treatment. Depot preparations could ensure continuous drug delivery, overcome bioavailability problems and avoid the risk of overdose with oral medications. However, depot preparations do not

allow flexibility in administration and dose adjustment. Patients may also complain of side effects at site of injection e.g. pain, oedema, pruritus and sometimes a palpable mass.

a. Depot vs oral

Evidence showed no difference between depot preparations with oral APs:

- flupenthixol decanoate vs penfluridol (attrition rates (OR=2.87, 95% CI 0.4 to 21) and usage of additional anticholinergic drugs (OR=1.5, 95% CI 0.5 to 4.2))^{36, level 1}
- fluphenazine decanoate vs oral APs (relapse rates within 26-52 weeks (RR=1.46, 95% CI 0.8 to 2.8), but less movement disorders in people on fluphenazine decanoate (NNH=14, 95% CI 10 to 82))^{37, level 1}
- depot risperidone vs oral risperidone (global improvement (RR=1.06, 95% CI 0.92 to 1.22) and adverse effects (RR=1.04, 95% CI 0.91 to 1.18))^{38, level 1}

b. Depot vs depot

Evidence showed the following:

- flupenthixol decanoate vs other depots showed no differences in outcomes e.g. relapse rate (OR=1.16, 95% CI 0.7 to 1.9) or leaving the study early (OR=1, 95% CI 0.6 to 1.7), significant less general movement disorders (OR=0.23, 95% CI 0.08 to 0.7) but no difference in tremor (OR=1.2, 95% CI 0.3 to 4) and tardive dyskinesia (OR=1.60, 95% CI 0.4 to 6)^{36, level 1}
- fluphenazine decanoate vs other depots had no difference in relapse rate within 26-52 weeks (RR=0.82, 95% CI 0.6 to 1.2)^{37, level 1}
- zuclopenthixol decanoate vs other depots had no difference in relapse rate (NNT=8, 95% CI 5 to 53), but zuclopenthixol decanoate induced more adverse effects (NNH=5, 95% CI 3 to 31) and also decreased the need for anticholinergic medication (NNT=9, 95% CI 5 to 38)^{39, level 1}

c. Dosage of depots

Evidence showed the following:

- low doses was as effective as standard doses (RR=2.09, 95% CI 0.6 to 7.1)^{37, level 1}
- no advantage of high doses over standard doses (OR=0.32, 95% CI 0.09 to 1.2)^{36, level 1}

Standard dose of depots:

- fluphenazine decanoate (modecate ®) = 25 mg every 2-4 weeks
- flupenthixol decanoate (fluanxol ®) = 40 mg every 2-4 weeks
- zuclopenthixol decanoate (clopixol ®) = 200 mg every 2-4 weeks
- risperidone (risperdal consta ®) = 25-50 mg every 2 weeks

Recommendation

- Depot preparations should be the treatment of choice when treatment adherence is an issue. **(Grade B)**
- Depot should be given not more than the standard recommended dosage. **(Grade A)**
- For safe practice, test doses should be used as set out in Appendix 4. **(Grade C)**
- All depot preparations are equally effective. **(Grade A)**

2.6 TREATMENT RESISTANT SCHIZOPHRENIA

About 25 percent of people with schizophrenia given APs will have either a partial or no response to treatment. ^{5, level 9} The pharmacological basis for this non-response remains unclear and may be due to lower sensitivities to dopamine blockade, dopamine receptor abnormalities, different metabolism of APs or different pharmacological responses. ^{16, level 1}

Treatment resistant schizophrenia (TRS) has been defined as failure of improvement of the target symptoms (positive, negative and/or cognitive) despite an adequate trial of medication for at least 6–8 weeks with adequate dosing, of at least two groups of APs. ¹⁶

There are many strategies that have been recommended by different guidelines in the management of TRS. ^{17, level 1; 40, level 1; 41, level 9; 42, level 1} As yet, there is no clear agreement on how or which order of APs to use. It is agreed generally that for people with schizophrenia with poor compliance, depot injection should be considered before concluding that the person is treatment resistant. Among the strategies are increasing the dosage of APs, switching to another AP of a different class, combining with another AP or adding adjunct medications e.g. mood stabilizer, antidepressant or benzodiazepine. There must be at least two trials of APs (one of which include a trial of AAPs) of adequate dosage and duration of treatment. ^{16, level}

¹ Compliance, substance abuse, concurrent medication use and physical illness must also be addressed. Clozapine remains the treatment of choice in people with TRS.

A meta-analysis of 12 RCTs, seven of which comparing clozapine to conventional APs, found clozapine superior in both efficacy and safety (NNT=4).^{43, level 1} This superiority of clozapine was further confirmed by another meta-analysis (NNT=5, 95% CI 4 to 6).^{44, level 1}

When clozapine was compared to other AAPs in TRS, the intent-to-treat analysis was not significant in quality of life score (3.63 points, 95% CI 0.46 to 7.71). However, clozapine was significantly superior in PANSS total score reduction (-4.93 points, 95% CI -8.82 to -1.05).^{21,45, level 2}

Recommendation

- Before starting clozapine, trial of two different APs (one of which should be AAPs) should be used with adequate dose and duration, and treatment adherence ensured. **(Grade A)**
- Other causes of non-response (comorbid substance misuse, poor treatment adherence, the concurrent use of other prescribed medicines, and physical illness) should be excluded. **(Grade A)**
- When TRS is established, clozapine should be used as early as possible. **(Grade A)**
- The use of clozapine should adhere to the manufacturer's prescription and monitoring protocol. **(Grade C)**

2.7 COMBINATION OF ANTIPSYCHOTICS

Combined therapy refers to the simultaneous administration of more than one AP. Various combinations being used include adding pimozide, sulpiride, olanzapine, loxapine and risperidone.^{16, level 1}

Combination of APs may be prescribed to individuals for a variety of reasons:

- During switching from one oral AP to another
- Addition of oral APs to those on depot treatment experiencing a relapse
- Lack of response to a single AP

The use of combined APs when compared to single AP in patient with schizophrenia was associated with better efficacy (NNT=7, 95% CI 4 to 17) and less all-cause discontinuation (RR=0.65, 95% CI 0.54 to 0.78).^{46, level 1} Further analysis of the 19 studies included in the meta-analysis showed that combination was effective in the following situations: using combination treatment at the onset (co-starting), combination using clozapine, trial duration more or equal to 10 weeks and combining AAP and conventional AP. However, most of the positive findings in the study were based on trials done in China and the study also detected a possibility of publication bias and heterogeneity of data. Eleven studies that recorded side effects found no group differences in terms of movement disorders, use of anticholinergic medications and their side effects, level of arousal, cardiovascular problems, central nervous system effects, endocrine disorders, gastrointestinal side effects, weight gain, and haematology and other laboratory values.

Recommendation

- Pharmacological treatment of schizophrenia should be monotherapy except during change over from one AP to another. **(Grade C)**
- Combination with clozapine may be considered. **(Grade A)**

2.8 USE OF ANTIPSYCHOTIC IN PREGNANCY AND DURING LACTATION

Little is known of the effects of perinatal exposure to typical or atypical APs. Most of the guidelines do not address the issue of using APs during pregnancy and lactation. The risk of using APs in pregnancy is an important issue to be addressed. Weighing the risks and benefits of treating mother with APs requires assessment of clinical effectiveness versus the risk of toxicity to the mother and her unborn child. Continuing APs in pregnant mother is preferable considering the risk of relapse without medication which can cause disruption in her life with accompanying poor personal and antenatal care, as well as suicidal and homicidal tendency. Untreated psychosis in mother also carries some risks to the fetus in terms of poor intrauterine growth and teratogenicity.^{47, level 1} Furthermore, the ill mother will have difficulties in bonding and caring for the newborn baby after delivery. Using alternative therapy e.g. cognitive behavioural therapy (CBT) or electroconvulsive therapy (ECT) for schizophrenia in pregnant mother remains unproven.

- Prolonged untreated episode of mental illness has adverse effects on both mother and infant.
- The decision to breast feed while taking APs should include the following considerations:
 - Adverse effects of untreated illness in mother
 - Risk of infant exposure to APs in breast milk
 - Benefits of breast feeding to infant and mother
 - Wishes of the mother

A SR found no RCT which compared the effects of any type of APs treatment with other treatment options (including standard psychosocial care, ECT or CBT) in pregnant women or during the postpartum period. ^{47, level 1} The lack of RCT is understandable in this condition considering the serious clinical and ethical dilemma.

In a cohort study of 151 mothers exposed to olanzapine (n=60), risperidone (n=49), quetiapine (n=36) and clozapine (n=6), it was noted that there was no significant differences in the rate of spontaneous abortion, stillbirth, pre-term delivery and malformation in the exposed group. ^{48, level 6} However, the study found higher but non-significant number of low birth weight babies in the exposed group compared to the unexposed group. In a case-control study, it was demonstrated that there was possible association between in-utero exposure to atypical APs and increased birth weight particularly for olanzapine and clozapine ($p < 0.05$). ^{49, level 7}

Gentile reported that out of 96 exposed pregnant patients to olanzapine, 71.9% delivered a healthy offspring and this was comparable with the general population (71.5%). ^{50, level 8} However, the exposed group had higher incidence of still birth (3.1% vs 2.0%) and fetal malformations (8.3% vs 3.8%). Amongst 11 exposed mothers to risperidone, 63.6% gave birth to healthy off springs but there was 9.1% congenital malformation. Clozapine had the biggest group of exposed mothers with 176 cases. The incidence of healthy off spring among the exposed mothers was lower (53.4% vs 71.5%). There were higher malformations (10.2% vs 3.8%). Quetiapine had very limited data with 3 cases of exposed mother which none developed any complications. There was lack of human data on the use of ziprasidone or aripiprazole in pregnant mothers. Animal studies demonstrated their possible teratogenicity. For a list of congenital malformations, refer to **Appendix 4.**

In the same review, Gentile also reported adverse drug reactions (ADR) in infants breast fed by mothers exposed to AAPs.^{50, level 8} For a list of effects of infant exposure to AAPs, refer to **Appendix 4**.

In a SR, it was noted that the exposure to low dose chlorpromazine in the first trimester of pregnancy resulted in an increase of congenital anomalies by 0.4%.^{51, level 1} This was not seen with trifluoperazine or haloperidol. The use of typical APs in the third trimester was associated with neonatal restlessness, tremor, poor suckling, abnormal movements, jaundice and functional bowel obstruction. There was no behavioural abnormality reported in exposed group to chlorpromazine five years later.

Some APs will be excreted in the breast milk. In a series of 34 cases of infants exposed to APs in breast milk, 25 showed no adverse effects.^{52, level 8} Refer to **Appendix 4** for details.

Recommendation

- Multidisciplinary care is recommended when managing a pregnant woman with schizophrenia. This involves psychiatrist, obstetrician, paediatrician and primary care physician. **(Grade C)**
- Before using AP in pregnant woman, the benefit and harm must be discussed with the patient and family. **(Grade C)**
- If AP is to be continued during pregnancy, a single AP should be used at the lowest effective dosage instead of multiple medications. **(Grade C)**
- Use high potency APs agent e.g. haloperidol or trifluoperazine to minimise maternal anticholinergic, hypotensive and antihistamine effect. **(Grade C)**
- Use of depot preparation e.g. fluphenazine decanoate during pregnancy should be avoided in order to limit the duration of any possible toxic effect to the foetus. **(Grade C)**
- Regular clinical monitoring seems to be the best approach to minimise APs exposure to breastfed infant. **(Grade C)**
- Before the mother is started on APs, her baby should be assessed on his behaviour, sleep, feeding pattern and alert level. **(Grade C)**
- The paediatrician and primary care physician should be well-informed about the side effects of APs and interactions with other commonly used medications in infants e.g. antibiotics, paracetamol and antihistamines. **(Grade C)**
- Formula supplementation may be used to reduce infant exposure after APs consumption by mother. **(Grade C)**

3. ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) continues to be used in a substantial number of people with schizophrenia. ^{53, level 8}

ECT may be used to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening e.g. in:

- Catatonic schizophrenia
- Schizophrenia with prominent affective symptoms
- Schizophrenia with previous history of improvement with ECT

3.1 CLINICAL EFFECTIVENESS

a. Real ECT versus control group (sham ECT or placebo)

In a meta-analysis of 12 RCTs, it was demonstrated that ECT significantly improved the clinical global improvement as compared to control group (NNT=6, 95% CI 4 to 12). ^{54, level 1}

b. ECT versus APs

The same meta-analysis noted that patients who received APs with ECT improved better than those who received ECT alone. (RR=2.18, 95% CI 1.3 to 3.6 for dichotomous data and RR=1.98 95% CI 0.97 to 4 for homogenous data). ^{54, level 1}

In a SR of 12 RCTs, it was demonstrated that there was no evidence to support ECT as an alternative to neuroleptics in terms of efficacy, response rate, hospital readmission or stay. ^{55, level 1} There was also no evidence to support the effectiveness of ECT as an adjunct treatment in schizophrenia.

Another SR noted limited evidence regarding the efficacy of ECT in schizophrenia and mania, and no RCT on the effectiveness of ECT in catatonia. ^{56, level 1} ECT either combined with APs or as a monotherapy was not more effective than APs. In patient with treatment-resistant schizophrenia who did not respond to clozapine, adding ECT may be a cost-effective option compared to adding chlorpromazine/haloperidol.

c. ECT combined with antipsychotic versus antipsychotic alone

The addition of ECT to APs showed a non-significant trend in favouring this combination as compared to APs alone (RR=0.76, 95% CI 0.52 to 1.1). ^{54, level 1}

d. ECT dose

It was also found that those who received twice the seizure threshold (2T) needed fewer doses of ECT to attain remission than those given the threshold doses (WMD=6.1, 95% CI 2.4 to 10). Those given four times the seizure threshold (4T) dose will also improve faster than threshold dose (WMD=9.4, 95% CI 6.3 to 12.5). However, treatment with 4T was non-superior to 2T (WMD=3.23, 95% CI 0.8 to 5.6). ^{54, level 1; 56, level 1}

e. Frequency of administration

There was no difference in efficacy between giving ECT three or five times a week. ^{54, level 1; 56, level 1}

Recommendation

- Use of ECT is not recommended in the general management of schizophrenia. **(Grade A)**
- ECT should not replace AP in acute management of schizophrenia. **(Grade A)**
- ECT should not be used in long-term management of schizophrenia. **(Grade A)**
- ECT may be used as an adjunct treatment with clozapine in patient who fail to response to clozapine alone in treatment resistant schizophrenia. **(Grade B)**
- Giving ECT thrice per week is as effective as giving it five times a week. **(Grade A)**
- Dose of ECT is twice of the seizure threshold and higher doses confer no advantage. **(Grade A)**
- ECT may be used to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening **(Grade C)** e.g. in:
 - Catatonic schizophrenia
 - Schizophrenia with prominent affective symptoms
 - Schizophrenia with previous history of improvement with ECT

4. PSYCHOSOCIAL INTERVENTION

Psychosocial treatment is an integral part of managing people with schizophrenia because of high relapse rates even when medication was adhered to ^{57, level 1}, persistence of symptoms despite continuous medications ^{18, level 1}, high rates of discontinuing medications ^{19, level 2} and no difference in quality of life with current available medications. ^{21, level 1} It had been shown that psychosocial and pharmacological treatment did better than pharmacological treatment alone. ^{58, level 1}

- Psychosocial interventions have the following objectives:
 - Improve the individual's ability to handle stressful life events
 - Increase adherence to medication
 - Help with illness self-management
 - Promote better communication and coping skills
 - Enhance quality of life
 - Promote recovery and reintegration
- Types of psychosocial intervention:
 - Family intervention
 - Psychoeducation
 - Social skills training
 - Cognitive remediation therapy (CRT)
 - Cognitive behaviour therapy (CBT)
 - Counseling and supportive psychotherapy

4.1 FAMILY INTERVENTION

Family intervention is an integral part in the psychosocial management of schizophrenia. It is aimed to improve family atmosphere and functioning, provide emotional support to family members and help with limits setting.

Family intervention includes the following ⁵⁹:

- Psychoeducation
- Teaching communication skills and problem solving
- Helping family to deal with stress
- Early warning sign recognition
- Crisis management

NICE 2003 recommended family intervention programmes in the following situations ^{16, level 1}:

- Families living with people with schizophrenia
- Families of people with schizophrenia who have recently relapsed or who are considered at risk of relapse
- Families of people with schizophrenia who have persisting symptoms

A Cochrane SR with 4,124 participants demonstrated that family intervention improved compliance with medication (NNT 7), decrease relapse rates (NNT 8), and reduced hospital admission (NNT 8). ^{59, level 1}

Recommendation

- Family intervention should be made available to all families of people with schizophrenia. **(Grade A)**

4.2 PSYCHOEDUCATION

In Malaysia, a psychoeducation package is available which covers aspects of illness, treatment and side effects of medications, role of the family, maintaining wellness and managing crisis. ^{15, level 9} It aims to change the behaviour and attitudes of the patients.

- Psychoeducation provides information and education regarding their illness to people with schizophrenia.
- Providing accurate information is important because of the long-term nature of the illness.
- Psychoeducation includes patient teaching, patient instruction or patient education and involve any provision to people with schizophrenia and their carers of information, support and the management strategies used in the treatment of schizophrenia.
- Psychoeducation should also include information and strategies to combat stigma and discrimination.

In a Cochrane SR of ten RCTs, it was noted that there was improvement in compliance with medication and reduction in relapse rates in those offered psychoeducation (NNT=6) versus standard care. Psychoeducational intervention also significantly lowered the readmission rates. ^{60, level 1}

Recommendation

- Use of psychoeducation as part of an overall package of multimodal psychosocial intervention should be offered in the treatment. **(Grade A)**
- Health professionals should provide information and treatment to people with schizophrenia and their carers; this should be considered an essential part of the routine treatment and management of schizophrenia. **(Grade C)**

4.3 SOCIAL SKILLS TRAINING

People with schizophrenia exhibit social skills deficits. Improving these will be a key factor in intervention. Social skills training will help improve social competence, role functioning and community reintegration. ^{16, level 1}

- Social skills training consists of practicing specific skills such as self-care, conversation skills, conflict handling, making friends, and assertiveness. ¹⁶
- Social skills training involves assessment of individual's social skills, followed by individual and/or group interventions using positive reinforcement, goal setting, modeling and shaping. ¹⁶
- The training initially involves smaller social tasks (such as responses to non-verbal social cues), and gradually built up into more complex social skills such as conducting a meaningful conversation. ¹⁶

Social skills training consistently led to improvement in social skills and social functioning (NNT=3), reduced general psychopathology (NNT=9) and decreased hospitalisation rates (NNT=5). ^{61, level 1}

In a large RCT study of structured social skills training, people with schizophrenia improved in terms of social functioning, insight and psychiatric symptoms; the re-employment rate was significantly higher, while relapse and rehospitalisation rates were significantly lower in the intervention group and this persisted for 24 months (NNT=2). ^{62, level 2} In another RCT of 78 patients, social skills training improved conversational (NNT=4) and assertive skills (NNT=3). ^{63, level 3}

Recommendation

- Social skills training is an important aspect of the multimodal approach and should be offered in routine psychosocial management. **(Grade A)**

4.4 COGNITIVE REMEDIATION THERAPY

Cognitive difficulties are prevalent in people with schizophrenia and these deficits impair psychosocial functioning. ^{61, level 1; 64, level 3} Specific deficits identified include memory problems, attention deficits and problems in executive functions. ^{64, level 3}

- Cognitive remediation therapy (CRT) is based on three general clinical principles, i.e. teaching new information processing strategies, individualising treatment and helping to transfer the improvement in cognitive function in real life setting. ⁶¹
- CRT involves task drills to improve cognitive deficits. ⁶⁴

In a review of 26 RCTs on the effectiveness of CRT published between 1968 to 2006, CRT was shown to have improved cognitive functioning in all cognitive domains apart from visual memory at post treatment (NNT=5) which increased further at an average of eight month follow up (NNT=3). ^{65, level 1} There were also notable improvements in social functioning (NNT=4) and general psychopathology (NNT=6). No evidence was available for suicide or relapse rates to discern the effects of duration or format for cognitive remediation but successful outcome of cognitive remediation is associated with higher intensity of treatment which is approximately 2 hours per week over 10 weeks. ^{66, level 8} A computerised cognitive remediation project (CREPS) for schizophrenia had been launched in Malaysia. ^{67, level 8}

Recommendation

- CRT may be offered as part of a multimodal psychosocial intervention. **(Grade A)**

4.5 COGNITIVE BEHAVIOURAL THERAPY

Beck introduced (CBT) for the treatment of depression. ^{68, level 9} The principles of CBT have been applied to many other psychiatric disorders including schizophrenia. The focus of CBT for people with psychosis is to help them cope with persistent delusions and hallucinations. ^{16, level 1; 69, level 9}

Components of a good CBT practice ⁷⁰:

- Ability to relate thoughts and feelings to current symptoms and distress
- Ability to correct misperceptions, irrational beliefs and reasoning biases related to current symptom
- Monitoring thoughts, feelings and behaviour with respect to the target symptom
- Promoting alternative ways of coping with the target symptom

A SR on CBT compared to standard care demonstrated the following ^{70, Level 1}:

- No difference in relapse and readmission rate (RR=0.29, 95% CI 0.1 to 1.8)
- Improved general psychological functioning in the short term (WMD=7.58, 95% CI 2.93 to 12.22) and medium term (WMD=12.6, 95% CI 5.8 to 19.43) but not in the long term (WMD=4.51, 95% CI -0.3 to 9.32)
- No significant difference in insight, attitudes to medication, and quality of life

When CBT was compared to supportive psychotherapy or other psycho-educational approaches, there was no significant difference in the global mental state and rates of readmission. ^{71, level 2}

Recommendation

- CBT for psychosis is not indicated for routine relapse prevention in people recovering from a recent relapse of psychosis and should be reserved for those with persistent distressing positive symptoms. **(Grade A)**

4.6 COUNSELLING AND SUPPORTIVE PSYCHOTHERAPY

The different types of psychotherapy in the treatment and management of schizophrenia have common factors such as time spent talking, client-focused, and supportive and caring relationship between therapist and patient in a broader therapeutic context. ^{16, level 1}

Counselling and supportive psychotherapy are psychological intervention which are facilitative, non-directive and/or relationship-focused, with the content of sessions largely based on clients' needs.

A recent Cochrane SR of 21 studies noted that there was no difference between supportive therapy and standard care.^{72, level 1} The main disadvantage of this review was the lack of quality studies and thus the authors were unable to form recommendations. More clinical trials on supportive therapy done by well-trained personnel are clearly indicated.

Recommendation

- Counselling and supportive psychotherapy may be offered as part of a multimodal psychosocial intervention. **(Grade C)**
- Counselling and supportive psychotherapy are not recommended as a sole intervention in the routine care of schizophrenia. **(Grade A)**

4.7 MULTIMODAL INTERVENTION

- Successful psychosocial rehabilitation requires improving self-care and social skills, building a good support and network as well as correcting cognitive deficits.⁷³
- Multimodal intervention refers to concurrent utilisation of family intervention, psychoeducation, social skills training and CRT as a package of rehabilitation activity.

In a meta-analysis evaluating effectiveness of multimodal intervention in adults with schizophrenia, the intervention was found to be superior to control groups i.e. placebo-attention conditions and standard care (post-therapy; NNT=5, at 8 months follow up; NNT=4).^{73, level 1} Multimodal intervention was also superior in the following subdomains: neurocognition (NNT=5), psychosocial functioning (NNT=6) and psychopathology (NNT=6).

Recommendation

- Effective rehabilitation should be multimodal in nature and offered as routine psychosocial intervention **(Grade A)**

4.8 TREATMENT ADHERENCE

Treatment adherence is a widely recognised problem but knowledge on how to improve it is still limited. Treatment non-adherence remains one of the greatest challenges in psychiatry. About 70-80% of people with schizophrenia had treatment non-adherence.^{74, level 8}

- Non-adherence includes failure to enter a treatment programme, early termination of therapy and incomplete implementation of instructions (including prescriptions). ⁷⁵
- Components of adherence intervention include ^{75; 76; 77}:
 - family intervention
 - psychoeducation
 - motivational interview
 - cognitive psychotherapy
 - compliance counselling
 - service level interventions e.g. ACT and CMHT
 - behavioural strategies:
 - appointment given before discharge from hospital
 - prompt in the forms of letters and telephone calls before appointment date
 - cue to remember taking daily medications

In a meta-analysis on treatment non-adherence, adherence interventions were more effective than usual care in promoting adherence (OR=2.59, 95% CI 2.21 to 3.03 for dichotomous outcomes and a standardised mean difference=0.36, 95% CI 0.06 to 0.66 for continuous outcomes). ^{75, level 1}

This finding is supported by two SR which concluded that psychosocial interventions must be accompanied by behavioural components (concrete problem-solving or motivational techniques) and service level interventions for effective treatment adherence. ^{76, level 1; 77, level 1}

Recommendation

- Combining psychosocial, service level interventions and behavioural strategies should be offered to improve treatment adherence. **(Grade A)**

5. SERVICE LEVEL INTERVENTION

This section in the CPG is of great relevance and importance in the Malaysian Mental Health services. The country is currently in the process of developing more comprehensive hospital-based community psychiatric services and mental health services at the primary care level. The services being reviewed in this guideline are community mental health teams, assertive community treatment, day hospital care, vocational rehabilitation, crisis intervention and home treatment team, and case management.

5.1 COMMUNITY MENTAL HEALTH TEAM

Community Mental Health Team (CMHT) is multidisciplinary team, comprising all the main professions involved in mental health, including nurse, assistant medical officer, occupational therapist, psychiatrist, clinical psychologist and social worker. ^{78, level 1}

CMHT has the following characteristics ⁷⁹:

- Multidisciplinary team of mental health staff
- Provide assessment, treatment and care to a defined population
- Provide the full range of specialist services
- Consultation to primary care staff
- Early relapse prevention
- Continuing care of patients with longer term disabilities
- May be supplemented by other specialised services e.g. home treatment in crisis and assertive community treatment

The 'standard' or 'usual' care that was used as comparator in this review included the non-team community care, outpatient care and hospital admissions. ^{78, level 1}

NICE found little evidence to show that CMHT was an effective way of organizing services. ^{16, level 1} Evidence of the effectiveness of CMHT in the management of schizophrenia is insufficient to make any evidence-based recommendations.

However, in a recent SR, CMHT was superior in promoting greater acceptance of treatment (NNT=4, 95% CI 3 to 11), reducing hospital admission (NNT=17, 95% CI 10 to 104) and fewer death by suicide but not statistically significant. ^{80, level 1} In this review, the three included studies had as comparator intervention that was focused on community-based assessment and multidisciplinary working.

Recommendation

- CMHT should be offered to promote greater acceptance of treatment. **(Grade A)**
- CMHT may be useful in people with repeated admission. **(Grade A)**

5.2 ASSERTIVE COMMUNITY TREATMENT

Assertive Community Treatment (ACT) is a well-defined model of service delivery, with the following aims:

- to keep people with serious mental health problems in contact with services
- to reduce the extent (and cost) of hospital admissions
- to improve outcomes (particularly quality of life and social functioning)

The following are key elements of ACT ⁸¹:

- Multidisciplinary care with involvement of psychiatrist
- Care provided for people with serious mental illness
- Shared responsibility for clients by team members
- Service provision by team, rather than brokerage of care
- Home-based or work-based care as much as possible
- Assertive nature of care to ensure follow-up
- Emphasis on medication adherence

NICE found that ACT compared with standard care is more likely to improve contact and satisfaction with services, decrease the use of hospital services, improve quality of life, and improve work and accommodation status. ^{16, level 1}

In a large RCT of 251 patients comparing ACT versus CMHT, ACT had no benefit over usual CMHT for inpatient admissions and clinical or social outcomes however satisfaction and engagement with services (NNT=6) may be greater for recipients of ACT. ^{82, level 2}

Recommendation

- ACT should be provided especially to those with little social support and have difficulty in engaging with CMHT services. **(Grade A)**

5.3 DAY HOSPITAL CARE

Day hospital care offer continuing care to people with schizophrenia who are not responsive to outpatient treatment alone. This has been used to improve clinical symptoms, reduce admission rates and enhance engagement. ^{83, level 1}

NICE found limited evidence on effectiveness of day hospital care. ^{16, level 1} A search for recent RCTs after June 2003 did not reveal any new studies of day hospital care.

Recommendation

- There was insufficient evidence to make any recommendation on day hospital care activities in Malaysia. **(Grade A)**

5.4 SUPPORTED EMPLOYMENT

The commonly used model of vocational rehabilitation is the ‘train and place’ model where people with schizophrenia are trained for a period of time before they are placed in work settings. ^{84, level 1} The work settings can be exclusive for the mentally-ill people (non-integrated) or integrated in mainstream settings. The training is structured (i.e. they are not tailored according to the individual’s preferences) and sheltered workshops were the usual training grounds.

Supported Employment (SE) programmes have the following characteristics ⁸⁵:

- Immediate job placement in integrated mainstream work settings
- On-the-job training
- Job placement and support according to individuals’ interests
- Ongoing, continuous on-the-job support
- Collaboration between treatment team and employers/work supervisors

Individual Placement and Support (IPS) model is a manualised intervention that follows above-mentioned SE principles. IPS programmes are usually integrated within mental health settings so that people with schizophrenia have access to psychiatrists, psychologists, social workers, vocational specialists and other care providers. Co-workers and supervisors collaborate with the treatment team to provide optimal support for the employee. ^{84, level 1}

There were several RCTs that favoured IPS Programmes over the 'train-and-place' programmes in helping people with schizophrenia obtain competitive employment with NNT ranging from 3 to 4. ^{84, level 1; 85-87, level 2}

There was also evidence to show that IPS Programmes achieved better employment outcomes e.g. better competitive wages and improving job retention ($p < 0.001$). ^{85, level 2; 87, level 2}

The effectiveness of IPS was proven with double the rate of obtaining competitive employment, increase in job tenure and hours worked. A high rate of employment did not show a detrimental effect on clinical wellbeing and relapse (NNH=9, 95% CI 5 to 11). IPS workers seemed more able to find jobs for individuals with severe mental illness in unskilled, support positions (e.g. warehouse or catering work). ^{88, level 2} In the IPS model as described by Burns et. al., one IPS worker was designated to carry a work load of 25 people job placed.

Recommendation

IPS should be provided for those who wish to return to work or gain employment. **(Grade A)**

- Other work-related activities including vocational rehabilitation, transitional employment or sheltered workshop may be offered when individuals are unable to work or are unsuccessful in their attempts to find employment. **(Grade C)**

5.5 CRISIS INTERVENTION AND HOME TREATMENT TEAM

Crisis Intervention and Home Treatment Team (CIHTT) is a form of service that aims to avoid admitting acutely ill people to hospital by providing intensive home-based support. The aim of crisis intervention and home treatment is to prevent hospitalisation and deterioration of symptoms and stress.

The elements of CIHTT include ⁸⁹:

- A multidisciplinary team
- Available 24 hours a day
- Prompt detection of relapse
- Swift, time-limited, intense treatment at home or community setting
- Treatment includes:
 - medication
 - counselling
 - practical help with living skills
- Support for close family members
- Referral to other level of care after crisis resolved

NICE concluded that CIHTT is superior to standard hospital-based care in reducing admissions and shortening stay in hospital. It is also more acceptable than hospital-based care for acute crises. ^{16, level 1} CIHTT are less likely to lose contact with service users, and may also have a marginally better effect on some clinical outcomes.

Joy CB et. al. ^{89, level 1} found no new studies to add to the five studies already included in the earlier review. ^{90, level 1} All of the studies included crisis intervention as part of package of care. CIHTT was able to prevent 55% of admission and avoided repeat admissions (NNT=11, 95% CI 6 to 97). CIHTT reduced the number of people leaving the study early (NNT=13, 95% CI 7 to 130), reduced family burden (NNT=3, 95% CI 2 to 4), and was found to be a more satisfactory form of care for both patients and families.

A RCT noted that patients in the CIHTT were less likely to be admitted to the hospital (OR=0.19, 95% CI 0.11 to 0.32) and more satisfied with treatment ($p=0.002$). ^{91, level 2}

Recommendation

- CIHTT should be offered as part of a package of hospital-based community psychiatric services in Malaysia. **(Grade A)**

5.6 INTENSIVE CASE MANAGEMENT

Case management is a modality of service delivery for people with schizophrenia to ensure they continue maintaining contact with mental health services. It involves allocating the patient to a case manager who is usually a nurse. There are at least three ways of case management i.e. helping patient to link with other services ('brokerage'), Intensive Case Management (ICM) and the care programme approach (applicable mainly in the UK). Some psychiatric units in Malaysia are implementing ICM services.

ICM shares similar characteristics with ACT including ⁸⁸:

- Daily team meeting
- Multidisciplinary working with psychiatrist as full team member
- Shared workload
- Small caseload (1 case manager: 15 patients)
- 24-hours availability

NICE found no sufficient evidence to make any recommendation about ICM for routine use in the National Health Service in England and Wales. ^{16, level 1}

A SR of 5961 participants in RCTs of case management found that ICM can reduce readmission to hospital when it was high (coefficient -0.23, 95% CI -0.36 to -0.09); but not as successful when readmission rate was low. ^{88, level 1}

Recommendation

- ICM is a useful way to reduce hospital readmission rate. **(Grade A)**

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SEARCH STRATEGY

The following free text terms or MeSH terms were used either singly or in combination: (schizophrenia OR paranoid disorders OR hebephrenic* OR oligophreni* OR psychotic* OR psychosis OR psychoses OR schizophreniform or schizoaffective), “mental disorder*”, “mental health”, “risk factor”, (polypharmacy OR combination OR concurrent), (monotherapy OR single), antipsychotic, effective*, (risperidone OR aripiprazole OR clozapine OR ziprasidone OR olanzapine OR quetiapine), (haloperidol OR chlorpromazine OR perphenazine OR sulpiride OR trifluoperazine OR fluphenazine OR zuclopenthixol OR flupenthixol), (rapid OR acute OR escalation OR tranquilisation OR titration), agitation, “depot antipsychotic”, (aggression OR hostility), “relapse prevention” “cognitive function”, “mood symptoms”, suicide, “negative symptoms”, pregnancy, lactation, “risk assessment”, “family intervention”, (“improve patient functioning OR “improve family functioning” OR “quality of life patient” OR quality of life carers/family”, psycho-education, “problem solving skills”, (psychotherapy or psychological), “social skills training”, “electroconvulsive therapy”, “community mental health team”, “assertive community treatment”, daycare, “community care”, “home treatment”, “intensive case management”, “crisis intervention”, “supported employment”, “vocational rehabilitation program*”, “rehabilitation program*”, “individual placement support”, interface, primary, secondary, “nursing-based interventions”, (“traditional medicine” OR “complementary medicine” OR “oriental medicine” OR “Chinese medicine” OR “ayurvedic medicine” OR “Indian medicine”), acupuncture, “high dose vitamin therapy”, “treatment adherence”

CLINICAL QUESTIONS

1. What are the risk factors of developing schizophrenia?
2. Is combined AP more efficacious and tolerable than single AP therapy?
3. Are AAP(s) more effective compared to conventional AP(s) in achieving remission?
4. Are persistent negative symptoms, mood symptoms, aggressive symptoms, cognitive symptoms or suicidal symptoms reduced with antipsychotic treatment compared to treatment as usual?
5. Is rapid escalation of AP more effective than treatment as usual in acute episode of schizophrenia?
6. Are people with schizophrenia getting symptom reduction with depot antipsychotics?
7. Are AAP(s) more effective compared to conventional AP(s) to prevent relapse?
8. Is taking AP safe during pregnancy and lactation?
9. Is family intervention effective in improving function or quality of life?
10. Is psychoeducation effective in improving function or quality of life?
11. Is problem solving skill effective in improving function or quality of life?
12. Is psychotherapy effective?
13. Is cognitive remediation therapy effective?
14. Is social skills training effective in improving patient's functioning, family's functioning or quality of life?
15. Is electroconvulsive therapy (ECT) effective?
16. Is clozapine effective in the treatment resistant schizophrenia?
17. Is community mental health team (CMHT) better than assertive community treatment (ACT)?
18. Does home treatment or crisis intervention give better outcome as compared to treatment as usual?
19. Is acute and non-acute day hospital care effective?
20. Is supported employment effective?
21. Is interface between primary and secondary care effective?
22. Is alternative/complementary therapy effective?

DIAGNOSTIC CRITERIA

DSM-IV-TR Diagnostic Criteria for Schizophrenia ^{92, level 9}

A. *Characteristic symptoms:* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

- i. Delusions
- ii. Hallucinations
- iii. Disorganised speech (e.g., frequent derailment or incoherence)
- iv. Grossly disorganised or catatonic behaviour
- v. Negative symptoms, i.e., affective flattening, avolition

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. *Social/occupational dysfunction:*

- i. Work
 - ii. Interpersonal relations
 - iii. Self-care
- (Markedly below the level achieved prior to the onset)

C. *Duration:* Continuous signs of the disturbance persist for at least 6 months 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

D. *Schizoaffective and Mood Disorder exclusion:* Rule out Schizoaffective Disorder and Mood Disorder with Psychotic Features

E. *Substance abuse/other general medical condition exclusion:* Not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or other general medical condition

F. *Relationship to a Pervasive Developmental Disorder:* In those with history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated)

International Classification of Diseases-10 (ICD-10) 93, level 9

Schizophrenia

Characterized by

- distortions of thinking and perception
- inappropriate or blunted affect
- clear consciousness and intellectual capacity maintained
- certain cognitive deficits may evolve over time
- the most important psychopathological phenomena include
 - thought echo
 - thought insertion or withdrawal
 - thought broadcasting
 - delusional perception and delusions of control
 - influence of passivity
 - third person hallucination
 - negative symptoms

The course of schizophrenic disorders can be either continuous, or episodic with progressive or stable deficit, or there can be one or more episodes with complete or incomplete remission.

The following should be excluded

- bipolar disorder
- overt brain disease
- drug intoxication or withdrawal

Table 1. Suggested AP Dosages and Adverse Effects 42, level 1; 94, level 9; 95, level 9

Drug	Starting Dose	Titration	Target Dose or Range	Maximum Daily Dose	Antipsychotic Schedule	Side Effects	Selected Drug Interactions
Amisulpride (Solian)	50 mg/day	50-100 mg every 2-3 days	50-300 mg for negative symptoms, 400-800 mg for positive symptoms	1200 mg	Once daily. If more than 400 mg, twice daily	Insomnia Anxiety Agitation Somnolence Nausea Dry mouth Acute dystonia Galactorrhoea	Alcohol CNS suppressant Antihypertensive drugs
Aripiprazole (Abilify) Generic available	10-15 mg /day	None	10-30 mg /day	30 mg /day	Once daily	Agitation Constipation EPS Insomnia Nausea Somnolence	Carbamazepine Fluoxetine Ketoconazole Paroxetine Quinidine St John's Wort
Olanzapine (Zyprexa)	5-10 mg /day	5 mg/wk	10-20 mg /day	30 mg/day	Once daily	Constipation Dizziness Dry mouth IGT Hyperlipidaemia Increased appetite Sedation Weight gain	Carbamazepine Fluvoxamine Rifampicin Smoking St. John's Wort
Quetiapine (Seroquel)	50 mg/day	300 mg every 3-7 days	300-800 mg/day	800 mg/day	Twice daily	Dry mouth IGT Headache Hyperlipidaemia Increased appetite Orthostatic hypotension Sedation Weight gain	Erythromycin Fluconazole Ketoconazole Phenytoin Sodium valproate St. John's Wort
Paliperidone (Invega)	3 mg/day	3 mg every 2-3 days	6-12 mg/day	12 mg/day	Once in the morning	EPS IGT	Carbamazepine Cimetidine Fluoxetine
Risperidone (Risperdal) Generic available	1-2 mg/day	1 mg every 2-3 days	2-6 mg/day	8mg/day	Once daily	Galactorrhoea Hyperlipidaemia Menstrual irregularity Orthostatic	Paroxetine Phenytoin Rifampicin Tricyclic antidepressants (TCAs)
Risperidone microspheres long-acting injection (Consta)	25 mg /2 weeks	25-50 mg /2 weeks	25-50 mg every 2 weeks	Should not exceed 50 mg every 2 weeks	Once every 2 weeks	Hypotension Prolactin elevation Sedation Sexual dysfunction Tardive dyskinesia Weight gain	
Ziprasidone (Zeldox)	40-80 mg /day	20-40 mg every 2-3 days	80-160 mg /day	160mg/day	Once or twice daily	Dizziness ECG changes EPS Rash Sedation Vomiting	Carbamazepine Diuretics Moxifloxacin Quinidine Sotalol TCAs
Clozapine (Clozaril) Generic available	12.5 mg /day	*Refer Table 3	300-900 mg /day (serum level for doses >600 mg /day)	900mg/day	Twice daily	Agranulocytosis Excess salivation Fever IGT Hyperlipidaemia Increased appetite Myocarditis Orthostatic Hypotension Sedation Seizures Tachycardia Weight gain	Barbiturates Caffeine Carbamazepine Cimetidine Erythromycin Phenytoin Rifampin Ritonavir Smoking Serotonin Specific Reuptake Inhibitors (SSRIs) St John's Wort

Appendix 4 (cont...)

Drug	Starting Dose	Titration	Target Dose or Range	Maximum Daily Dose	Antipsychotic Schedule	Side Effects	Selected Drug Interactions
Chlorpromazine	50-100 mg/day	50-200mg/day	300-1000mg/day	1000mg/day	3 times daily	Constipation Dry mouth EPS Orthostatic hypotension Photosensitivity Sedation Tachycardia Tardive dyskinesia	Guanethidine Meperidine Paroxetine Pindolol Quinolones β -Blockers Ziprasidone
Perphenazine	4-8 mg/day	4-8 mg/day	16-64mg/day	64mg/day	3 times daily		Guanethidine Paroxetine Quinolones
Fluphenazine depot (Modecate) Generic available	12.5-25mg IM/ 1-3 weeks	12.5 mg /injection (test dose)	6.25-50 mg IM every 2-4 weeks	100 mg IM (per 4 weeks)	Every 1-3 weeks		Vitamin C Cisapride Potassium citrate Ziprasidone Levodopa Acetylcholinesterase inhibitors Quinolones
Flupenthixol decanoate (Fuanxol)	10-20 mg IM/ 1-3 weeks	10 mg per injection (test dose)	10-40 mg IM every 2-4 weeks	80 mg IM (per 4 weeks)	Every 1-3 weeks		Lithium Midodrine hydrochloride Alcohol Guanethidine Levodopa Metoclopramide Prochlorperazine
Haloperidol	2-5 mg/day	2-5 mg/day	2-20mg/day	20 mg/day	1 – 3 times daily		Azole antifungals Carbamazepine Rifabutin Rifampicin
Trifluoperazine	2-5 mg twice daily	2-5 mg every 3-7 days	5-20mg/day	40 mg/day	Twice daily		Alcohol Cisapride Guanethidine Metrizamide Paroxetine
Sulpiride Generic available	200-400 mg daily	200 mg every 3-7 days	400-800 mg daily	1600 mg	Twice daily		Midodrine hydrochloride Levodopa Alcohol
Zuclopthixol acetate (Acuphase)	50-100 mg IM/2-3 days	-	50-200 mg /72 hours	Not to exceed 200 mg in 72 hours	-		Alcohol Barbiturates Guanethidine Metoclopramide Piperazine Levodopa
Zuclopthixol decanoate (Clopixol depot)	100-200 mg IM/1-3 weeks	100-200mg /injection	100-400 mg /1-3 weeks	600 mg every four weeks	Every 1-3 weeks		

Table 2. Chlorpromazine Equivalents ^{40, level 1}

Name of AP	APs Recommended Dose Range (mg/day)	Chlorpromazine Equivalents (mg/day) ^a	Half-Life (hours) ^b
Chlorpromazine	300 – 1000	100	6
Fluphenazine	5 – 20	2	33
Perphenazine	16 – 64	10	10
Trifluoperazine	15 – 50	5	24
Haloperidol	5 – 20	2	21
Aripiprazole	10 – 30	7.5	75
Clozapine	150 – 600	-	12
Olanzapine	10 – 30	5	33
Quetiapine	300 – 800	75	6
Risperidone	2 – 8	2	24
Ziprasidone	120 – 200	60	7

^a Chlorpromazine equivalents represent the approximate dose equivalent to 100 mg of chlorpromazine (relative potency).

^b The half-life of a drug is the amount of time required for the plasma drug concentration to decrease by one-half; half-life can be used to determine the appropriate dosing interval. It does not include the half-life of its active metabolites.

***Table 3. Clozapine Dosing Schedule** ^{42, level 1}

Day	Dosage
Day 1	12.5 mg daily
Day 2	25 mg daily
Day 3	25 mg twice daily
Day 6	25 mg at morning, 50 mg at evening
Day 9	50 mg twice daily
Day 12	75 mg twice daily
Day 15	100 mg twice daily
Day 18	125 mg twice daily
Day 21	150 mg twice daily
Day 24	100 mg at morning, 200 mg at evening

* Dose adjustments based on targeted symptoms (positive, negative and cognitive) and tolerability

Table 4. Patient Monitoring Parameters ^{14, level 9; 42, level 1}

Test	Remark
BMI	At every visit
Blood pressure and pulse rate	At every visit
Side effects	At every visit (follow Senarai Semak Kesan Sampingan Ubat-ubatan Psikotropik/PKM 17/2001 PIN 2003)
Electrocardiogram	At least one for patient more than 40 years old or as clinically indicated
Total White Blood Count	a. upon starting AP b. for clozapine: <ul style="list-style-type: none"> • every week for first 18 weeks • every month after that for the first year • every visit subsequently
Fasting plasma glucose level or hemoglobin A1c	a. upon starting AP treatment and yearly b. if patient has risk factor for Diabetes Mellitus, upon starting, at four months and yearly
Lipid screening	a. upon starting and every two years if lipid levels normal b. if Low Density Lipoprotein (LDL) level is > 3.3.mmol/l, every 6 months
Pregnancy test	As clinically indicated

Table 5. AAPs: Comparison of Adverse Reactions ^{94, level 9; 96, level 9; 97, level 9}

Drugs	Agranulocytosis	Anticholinergic effects	EPS at low doses	Dose dependent EPS	Orthostatic hypotension	Prolactin elevation	Sedation	Tardive dys-kinesia	Weight Gain
Conventional antipsychotics	± to +	± to +++	± to ++	+++	+ to +++	++ to +++	+ to +++	+++	± to ++
Clozapine	++	+++	±	-	+++	-	+++	-	+++
Risperidone	±	±	±	++	+ to +++	++ to +++	+	±	++
Olanzapine	±	+	±	+	+	±	++	±	+++
Quetiapine	±	±	±	-	++	±	++	±	+ to ++
Ziprasidone	±	±	±	+	+	+	+	±	±
Aripiprazole	±	+	+	++ *	+	±	±	±	+
Amisulpride	±	±	±	++	+	++ to +++	+	±	+

- =Absent, ± =Minimal, + =Mild/Low Risk, ++ =Moderate Risk, +++ =Severe/High Risk

* Especially doses higher than 10mg may cause akathisia and activation in some patients

Table 6. Fetal and Perinatal Complications and Adverse Drug Reactions in Breastfed Infants with the Use of AAPs ^{50, level 8}

Drug	Major/minor fetal malformation plus perinatal complication	ADRs in Breastfed Infants
Olanzapine	<ul style="list-style-type: none"> • One unilateral dysplastic kidney • One Down's Syndrome • One infant death • Four gestational diabetes (GDM) with two complicated by hypertension and pre-eclampsia 	Jaundice, sedation, cardiomegaly, heart murmur, shaking, poor suckling, lethargy, protruded tongue, rashes, diarrhea, sleeping disorder
Quetiapine	Three cases without complications	One case of bipolar mood disorder with normal baby
Risperidone	<ul style="list-style-type: none"> • One agenesis of corpus callosum 	Three cases - no metabolite of risperidone found in breast milk (Two of them breast-fed and without ADR)
Clozapine	<ul style="list-style-type: none"> • One leukocytosis and slight decreased of hemoglobin • One intrauterine death • Four cases of newly-onset or worsening GDM • Others include floppy infant syndrome, neonatal seizures, gastro-esophageal reflux disease, and clozapine-induced agranulocytosis in infants 	No mention of number of cases Reports on sedation, agranulocytosis and cardiovascular instability
Ziprasidone	Lack of human data but animal studies suggested developmental delays, possible teratogenic effect and increased stillbirth	No published information
Aripiprazole	Animal studies showed development of toxicity and teratogenic effect e.g. delayed skeletal ossification and decreased fetal weight	Excreted in animal's milk (Not known in human milk).

Table 7. Clinical Status of Infants on Exposure to APs ^{50, level 8}

Antipsychotics	Number of nursing infants	Clinical status of infants after exposure		
		Not reported	No ADR	ADR
Chlompromazine (CPZ)	14	0	10	4 ^{a,b}
Trifluoperazine	2	0	2	0
Perphenazine	1	0	1	0
Haloperidol (HPL)	11	1	7	3 ^b
Clozapine	1	1	0	0
Olanzapine	3	0	3	0 ^c

a - Lethargy (one case of patient was on CPZ)

b - Declining scores on sequential developmental testing (three on CPZ, one on HPL)

c - Cardiomegaly at birth in one baby exposed to olanzapine in utero. Breast feeding stopped at Day 7 postpartum but jaundice and somnolence persisted

LIST OF ABBREVIATIONS

AAP(s)	Atypical antipsychotic drug(s)
ACT	Assertive Community Treatment
ADR	Adverse drug reactions
AMS	Amisulpride
AP(s)	Antipsychotic drug(s)
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
CBT	Cognitive Behavioural Therapy
CMHT	Community Mental Health Team
CIHTT	Crisis Intervention and Home Treatment Team
CNS	Central nervous system
CPG	Clinical Practice Guidelines
CPZ	Chlorpromazine
CRT	Cognitive Remediation Therapy
DSM IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision
ECT	Electroconvulsive therapy
EPS	Extrapyramidal side effects
HTA	Health Technology Assessment
ICD-10	International Classification of Diseases (ICD) – Tenth Revision
ICM	Intensive Case Management
IGT	Impaired glucose tolerance
IM	Intramuscular
IV	Intravenous
IPS	Individual Placement and Support
MOH	Ministry of Health
NICE	National Institute for Clinical Excellence
NNH	Number needed to harm
NNT	Number needed to treat
OLZ	Olanzapine
OR	Odds ratio
PANSS	Positive and Negative Syndrome Scale
RCT(s)	Randomised clinical trial(s)
RR	Relative risk
SE	Supported Employment
SR	Systematic review
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
TRS	Treatment resistant schizophrenia
WMD	Weighted Mean Difference

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LEVELS OF EVIDENCE SCALE

LEVEL	STRENGTH OF EVIDENCE	STUDY DESIGN
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM THE CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT & RESEARCH, (CAHTAR) SPAIN

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)