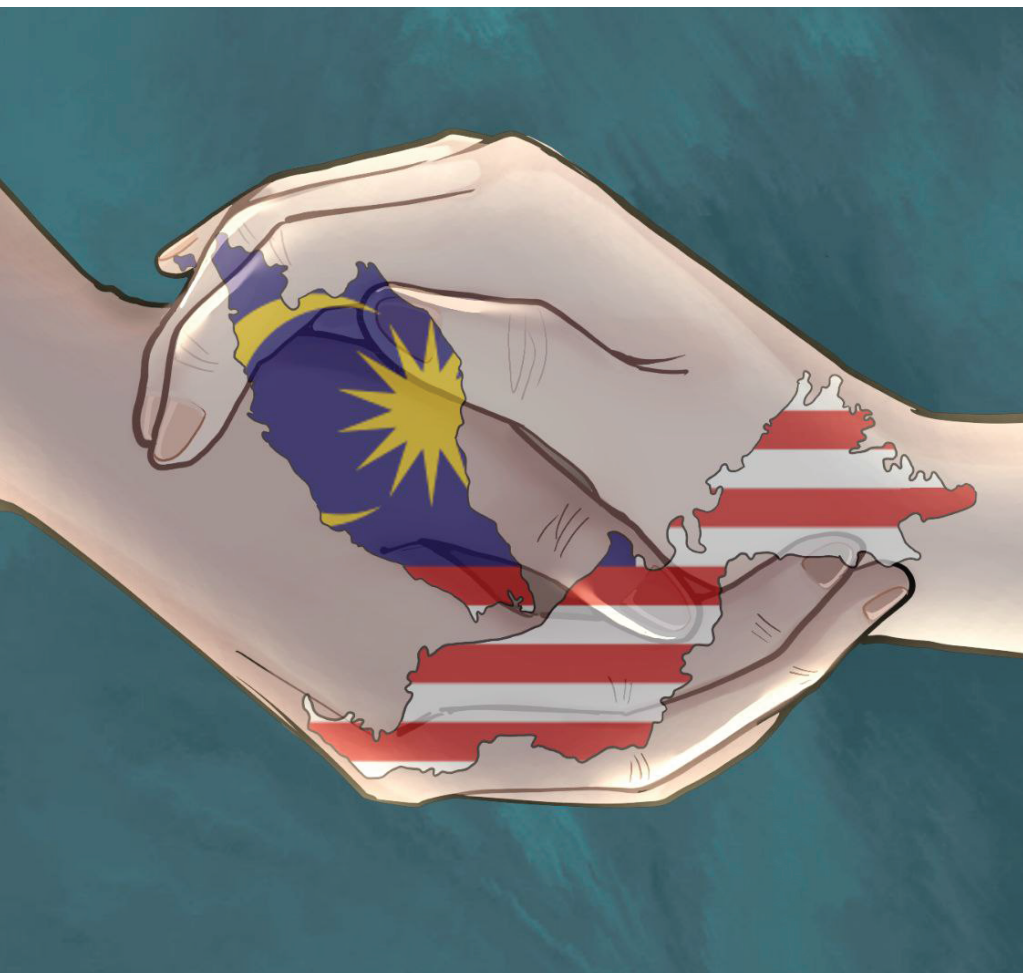
CLINICAL PRACTICE GUIDELINES

2021

MOH/P/PAK/467.21(GU)-e

MANAGEMENT OF SCHIZOPHRENIA

(SECOND EDITION)



Ministry of Health Malaysia

Malaysian Psychiatric Association

Academy of Medicine Malaysia

Published by:
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre 62590
Putrajaya, Malaysia

e-ISBN: 978-967-2887-32-4

Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my
https://www.psychiatry-malaysia.org

Also available as an app for Android and iOS platforms: MyMaHTAS

STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare 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.

UPDATING THE CPG

These guidelines were issued in 2021 and will be reviewed in a minimum period of four years (2025) or sooner if new evidence becomes available. When it is due for updating, the Chairperson of the CPG or National Advisor of the related specialty will be informed. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed, and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which will be the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

In this CPG the word ‘should’ is used to reflect a strong recommendation and ‘may’ to reflect a weaker recommendation.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

REFERRAL

- Early referral to psychiatric service should be considered for people with schizophrenia having diagnostic or treatment issues.

ASSESSMENT AND DIAGNOSIS

- People with possible schizophrenia should be assessed thoroughly by history taking, (self-report and collateral), physical examination, mental state examination and relevant investigations (if indicated).
- Schizophrenia should be diagnosed using either Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) or International Classification of Diseases and Related Health Problem 10th Revision (ICD-10).

TREATMENT

a. Pharmacological intervention

- Antipsychotics (APs) should be offered in schizophrenia as it is the mainstay of the treatment.
- Treatment adherence should be regularly monitored and maximised until the termination of treatment is indicated in schizophrenia.
- Long-acting (depot) injectable AP in schizophrenia:
  - should be offered when there is medication adherence issue
  - may be considered based on patient's preference
- APs should be offered to prevent relapse in schizophrenia.
  - Second-generation APs are the preferred choice.
  - Standard dose of APs should be considered as maintenance treatment.
- Intermittent treatment using APs should be avoided in schizophrenia.

b. Physical intervention

- Electroconvulsive therapy may be considered in schizophrenia to achieve rapid and short-term improvement of severe symptoms after an adequate trial of AP is proven ineffective and in treatment-resistant schizophrenia.

c. Psychosocial intervention

- Psychoeducation which includes early warning signs interventions should be given in addition to other interventions in schizophrenia.
- Supported employment should be offered in schizophrenia.
- Cognitive remediation therapy may be considered as an intervention for cognitive difficulties in schizophrenia.
- The following may be offered in schizophrenia:
  - social skills training
  - peer support
  - family therapy
  - cognitive behaviour therapy for psychosis

SERVICE LEVEL INTERVENTION

- Crisis intervention services should be offered to people with schizophrenia in acute phase.
- Assertive community treatment should be provided for people with schizophrenia who have difficulties engaging with the mental health services.
- Intensive case management should be considered for people with schizophrenia who are at risk of treatment non-adherence.
- Collaborative community-based service intervention may be offered for people with schizophrenia.
- Early intervention in psychosis service should be provided for people with first episode of psychosis.

TREATMENT OF TREATMENT-RESISTANT SCHIZOPHRENIA

- Clozapine should be offered in treatment-resistant schizophrenia.

CHALLENGES IN MANAGEMENT

- People with schizophrenia and co-morbid substance use disorder should be referred to a psychiatric service for further management.
- People with schizophrenia and smoking should be offered help with smoking cessation.
- Pre-pregnancy care which includes counselling should be offered to all women in reproductive age with schizophrenia.
- Multidisciplinary care should be offered in the management of pregnant women with schizophrenia.
- Clozapine may be considered in schizophrenia with persistent suicidal risk.
- Patient's rights in schizophrenia should be included in the training of healthcare providers and family members.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and Ministry of Higher Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. PubMed and Guidelines International Network (refer to **Appendix 1** for Example of Search Strategy). The search was limited to literature published on humans, "all adults (19 plus years)", publication from year "2009 to Current" and English language. In addition, the reference lists of all retrieved literature and guidelines were searched and, experts in the field contacted to identify relevant studies. All searches were conducted from 19 Nov 2018 to 26 Feb 2019. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 30 June 2021 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other CPGs on schizophrenia e.g.:

- Practice Guideline for The Treatment of Patients with Schizophrenia (Third Edition) [The American Psychiatric Association (APA), 2021]
- Psychosis and Schizophrenia in Adults [National Institute for Health and Care Excellence (NICE), 2014]
- Management of Schizophrenia [Scottish Intercollegiate Guidelines Network (SIGN), 2013]

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 35 clinical questions (CQ) were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for Clinical Questions). The DG members met 33 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed at each DG meeting. All statements and recommendations formulated were agreed upon by both the DG and

RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG was developed largely based on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634).

OBJECTIVES

The objectives of the CPG are to provide recommendations on the management of schizophrenia on following aspects:

a) early detection and referral
b) assessment and diagnosis
c) treatment and follow-up
d) challenges in management including special groups

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria
Adults (aged ≥18 years old) with a diagnosis of schizophrenia

TARGET GROUP/USERS

This document is intended to guide those involved in the management of schizophrenia at any healthcare level including:

i. doctors
ii. allied health professionals
iii. trainees and medical students
iv. patients and their advocates
v. professional organisations

HEALTHCARE SETTINGS

Primary, secondary and tertiary care settings

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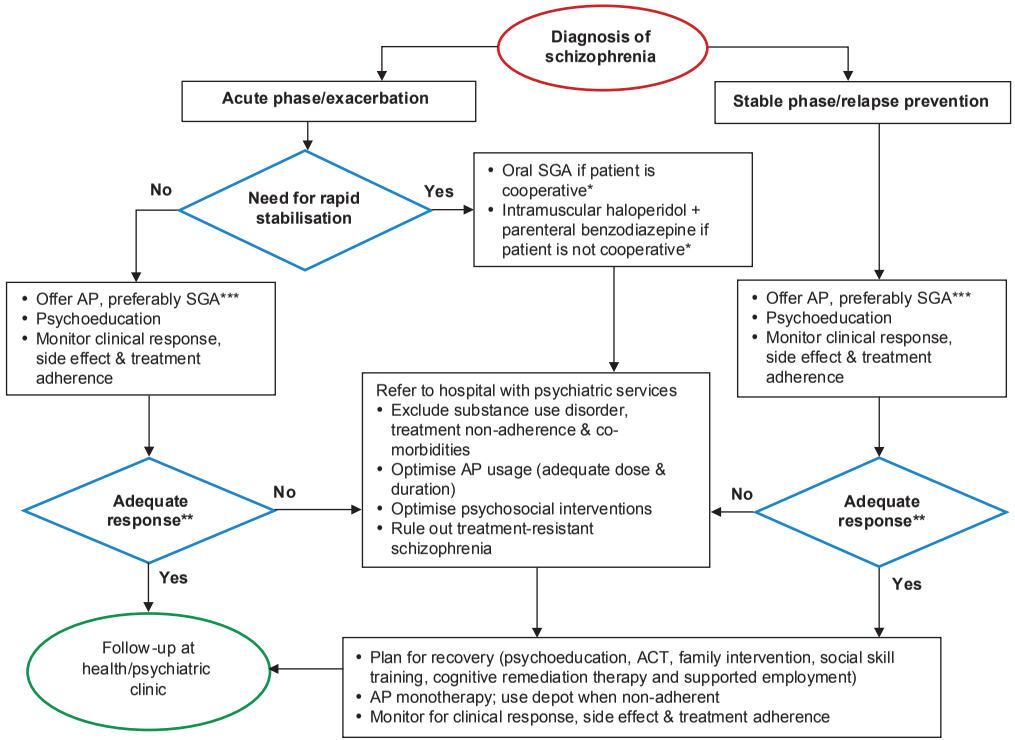
ALGORITHM 1. MANAGEMENT OF SCHIZOPHRENIA

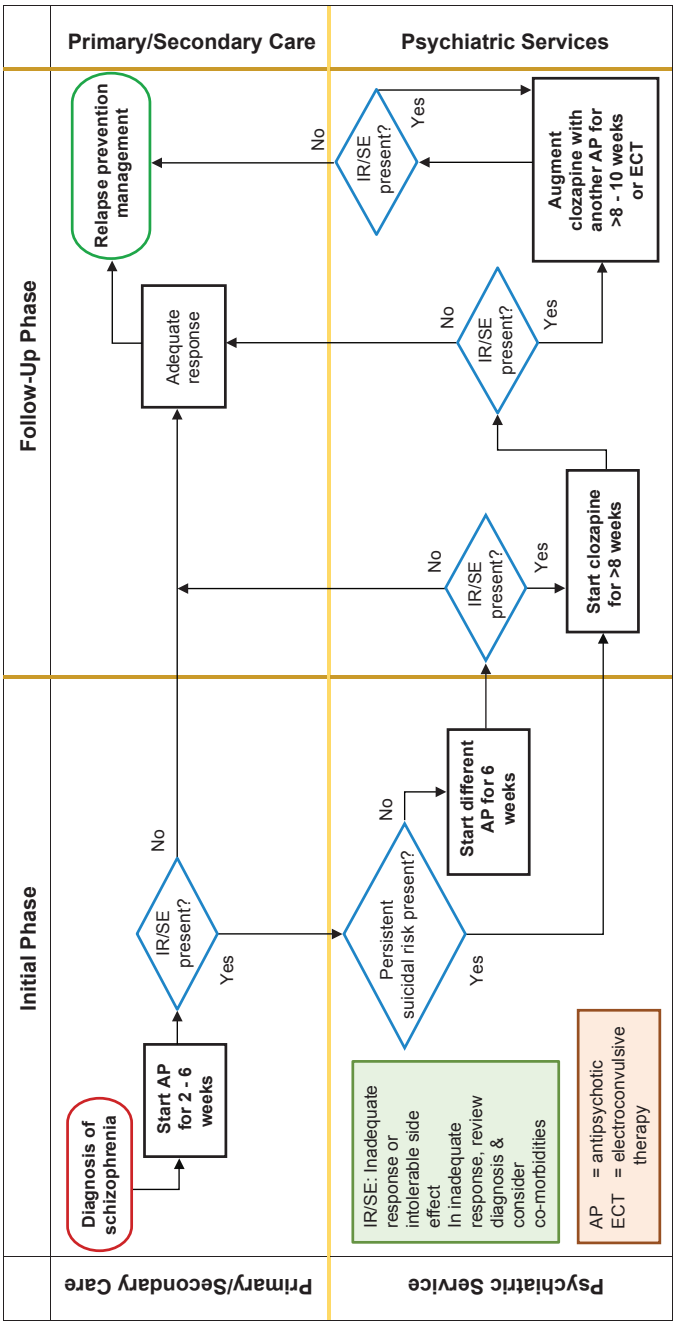


*Cases to be referred urgently to psychiatric services
**Adequate response: A reduction in symptoms as a result of treatment that is associated with clinically significant benefit in functioning and/or quality of life

***Prevention & management of side effect of AP at all phases
- Monitor EPS/akathisia/ weight gain/diabetes/ cardiovascular disease/ sexual dysfunction
- Follow schedule of physical care

AP = antipsychotic
SGA = second-generation AP
ACT = assertive community treatment
EPS = extrapyramidal side

ALGORITHM 2. PHARMACOTHERAPY FOR SCHIZOPHRENIA



1. INTRODUCTION

Schizophrenia is a term that describes a major psychiatric disorder that alters an individual's perception, thought, affect and behaviour. Globally, it was ranked as the 11th leading cause of disability in 2013.[1] In the Second Report of the National Mental Health Registry on Schizophrenia in 2003 to 2005, the incidence rate of schizophrenia in Malaysia was stated as 5 cases/100,000 population/year. However, the expected rate was 100 cases/100,000 population/year and possible reasons for low reported incidence were delayed or under reporting and administrative reasons. The duration of untreated psychosis (DUP) was long with a mean of 28.7 months and longer among females. The clinical importance of DUP was that it was one of the few prognostic factors which can be altered through changes in health service delivery.[2] This emphasises the value of early recognition and the necessity for early referral and intervention including during prodromal period.

Although the prevalence of schizophrenia worldwide was low,[3] its impact on health, social and economy are tremendous for patients, families/caregivers and society. In an economic evaluation in Malaysia, based on a total estimated number of treated cases of 15,104, the total economic burden of treatment for schizophrenia stood at USD100 million which was equivalent to 0.04% of the national gross domestic product. On average, the mean cost per patient was USD6,594. Of the total economic burden, 72% was attributed to indirect cost (USD72 million), followed by direct medical cost at 26% and the remaining on direct non-medical cost.[4] This huge magnitude of this disease burden is vital for policymakers to prioritise service for schizophrenia.

Worldwide, mental health services have experienced a series of paradigm shifts along with the development of medical technologies and the human rights movements where the services are delivered in the community.[5; 6] The community-based mental health service takes into account the fact that people with schizophrenia face difficulties in essential issues e.g. employment, housing, and relationship with families and friends,[6; 7] besides stigma and discrimination. Ideally, such service should include care and treatment delivered close to home.[8, level III] In Malaysia, efforts on integrating the care for mentally ill patients in the community have started since 1997 as outlined in the National Mental Health Policy.[9; 10] Subsequently, the development of community mental health centre (CMHC) begun in 2011. CMHC, or Mentari as it is branded in Malaysia, is a centre for treatment and care of mental health that offers screening, diagnosis, treatment and rehabilitation of any person suffering from any mental disorder in accordance with the Mental Health Act 2001 and Mental Health Regulation 2010.[11]

The holistic management of schizophrenia encompasses biological-psychosocial-spiritual approach to various dysfunction domains i.e. positive symptoms, negative symptoms, cognitive dysfunction, mood symptoms and motor symptoms. Since the first edition of Management of Schizophrenia in Adults in 2009, numerous advances in the management of mental disorder have developed including treatment targeting those who are difficult to treat or have intolerable to medications and non-adherence to treatment. In this edition of CPG, more clinical questions were added to address the advances. New issues being addressed are screening, early intervention in psychosis, special population and social issues. The summary on management and pharmacotherapy of schizophrenia are illustrated in **Algorithm 1** and **2**.

2. EARLY DETECTION AND REFERRAL

2.1 Risk Factor

Latest meta-analysis/systematic review showed significant risk factors for schizophrenia were:

a. substance-induced psychoses associated with cannabis, hallucinogens and amphetamines had an increased risk of transition to schizophrenia[12, level II-2]
b. increasing paternal age with RR ranging from 1.05 to 1.79[13, level II-2]
c. most urban environment compared with most rural environment (OR=2.37, 95% CI 2.01 to 2.81)[14, level II-2]
d. prenatal exposure to a range of infections and inflammatory responses may be a risk factor e.g. Herpes Simplex (HSV-2) with OR ranging from 1.5 to 1.8 and toxoplasma gondii (OR=1.79, 95% CI 1.01 to 3.15)[15, level II-2]

In a recent systemic review, there was a risk to develop schizophrenia in the offspring of mother with prenatal Toxoplasma gondii infection. Association with HSV-2 infection was likely due to confounding factor. In contrast, maternal influenza infection was a viable risk factor for schizophrenia.[16, level III] However, quality of the included primary papers were not mentioned.

Other risk factors would include:

- family history of schizophrenia[17]
- history of obstetric complications e.g. pre-eclampsia and extreme prematurity[17]
- cannabis use[17]
- history of childhood central nervous system infection[17]
- refugee and migrant status with HR of 2.90 (95% CI 2.31 to 3.64) and 1.75 (95% CI 1.51 to 2.02) respectively[18, level II-2]

2.2 Screening

A new 32-item self-rating screening tool (SPro) was developed for pre-psychotic states. SCL-90-R-PARA/PSYC was generated based on “Paranoid Ideation” (PARA) and “Psychoticism” (PSYC) subscales of Symptom-Checklist-90-Revised (SCL-90-R) to explore psychosis-like symptoms. A study examining predictive validity of SPro against SCL-90-R-PARA/PSYC on military men showed an AUC of 0.74 (95% CI 0.65 to 0.84).[19, level III]

In another study on preliminary validity of the brief version self-report Prodromal Questionnaire (PQ-B) among adolescents and young adults at two prodromal psychosis research clinics showed good validity of prodromal psychosis syndromes (AUC=0.78, 95% CI 0.70 to 0.84).[20, level III]

A two-stage study to screen relatives of people with schizophrenia and general individuals for sub-threshold psychosis used Screening Questionnaire (SQ) and General Health Questionnaires-12 (GHQ-12) in the initial stage. Those who screened positive were reassessed using the Comprehensive Assessment of At-Risk Mental State in the second stage. Of 29% people initially screened positive by both SQ and GHQ-12, only 4% were positive after final assessment. These indicated that both SQ and GHQ-12 were not suitable for screening early psychosis.[21, level III]

- More evidence is warranted before screening tools for pre-psychosis in schizophrenia can be recommended.
- 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.
- People with risk factors* in developing schizophrenia and with prodromal symptoms may require further assessment to rule out schizophrenia; this may be repeated if indicated over time.

*refer to **Subchapter 2.1**

2.3 Referral

Since the integration of mental health care into the primary care services in 1996,[10] most health facilities in Malaysia are able to provide mental health services that focus on mental health promotion and provide early detection and treatment for people with mental disorders. These facilities include the primary care clinics (both in the government and private sectors) and the district hospitals. The integration program underlines the importance of both the primary and tertiary centres working together to create a seamless pathway for people with mental illness in receiving care.

- For people with schizophrenia treated in primary care, early referral to psychiatric service should be considered in the following circumstances:[17; 22]
  - presence of prodromal or attenuated symptoms
  - unclear diagnosis
  - plan for psychosocial rehabilitation
  - treatment adherence issues
  - poor response to treatment
  - potential violent behaviour to self or others
  - intolerable side effects from medication
  - co-morbid substance use disorder
  - special group e.g. pregnancy, paediatric and geriatric age

For group of people at high risk of developing psychosis, emerging practices advocate that they should be referred for mental health assessment preferably to the early intervention services, e.g. person in distress with declining social function plus any of the following:[22]

- transient or attenuated psychotic symptoms
- experiences or behaviour suggestive of possible psychosis
- a first-degree relative with psychosis or schizophrenia

Recommendation 1

- Early referral to psychiatric service should be considered for people with schizophrenia having diagnostic or treatment issues*.

*refer to the preceding yellow box

In addition to the primary care clinics, the Community Mental Health Centres or Mentari also plays a role in screening and early intervention in mental illness including schizophrenia. Mentari offers walk-in services where people in the community who have symptoms of mental illness can visit nearby Mentari to have assessment done on them.[17]

3. ASSESSMENT AND DIAGNOSIS

3.1 Bio-Psychosocial Assessment

Bio-psychosocial assessment is essential in the diagnosis of schizophrenia. Established tools e.g. Mini International Neuropsychiatric Interview (MINI) and Structured Clinical Interview for DSM Disorders (SCID) are used for diagnosis, while Brief Psychiatric Rating Scales (BPRS) and Positive and Negative Symptoms Scale for Schizophrenia (PANSS) are performed for severity assessment. It can be used in both primary and secondary/tertiary care.

In two cross-sectional studies, Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV) showed κ value of >0.8 for diagnosis of schizophrenia with sensitivity and specificity >0.70.[23 - 24, level III]

New evidence on assessments for people with schizophrenia are discussed below:

- A small cross-sectional study showed Self-evaluation of Negative Symptoms had excellent psychometric properties in measuring the symptoms (Cronbach's α of 0.867 at baseline and 0.897 at 4 - 8 weeks).[25, level III]
- The 4-item Negative Symptom Assessment (NSA-4) on speech quantity, emotion, social drive and interest was effective in rapidly assessing negative symptoms in people with schizophrenia. It was not affected by geographic regions of practice, professional credentialing or their familiarity with the use of schizophrenia symptom rating instruments.[26, level III]
- A small validation study demonstrated that Personal and Social Performance (PSP) scale was significantly correlated with other similar functioning measures such as PANSS, Global Assessment of Functioning (GAF), Quality of Life Scale (QLS) and Clinical Global Impression Scale (CGI-S) with r of -0.31, 0.35, 0.37 and -0.27 respectively for construct validity at baseline. A stronger correlation between PSP and CGI-S at follow-up was noted with r= -0.60 in test-retest reliability.[27, level III] In another study on those with acute symptoms, PSP had good interclass reliability of 0.87. The correlations between baseline severity based on PANSS and CGI-S with PSP were also significant.[28, level I]
- Among neurocognitive assessments, the Brief Cognitive Assessment Tool for Schizophrenia (B-CATS) had an administration time of approximately 10 minutes. It correlated significantly (r=0.76) with widely used neurocognitive battery i.e. the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS).[29, level III]

- In a large multicentre validation study in people with schizophrenia, Brief Negative Symptom Scale showed excellent internal consistency (Cronbach's α=0.94), strong correlation with the PANSS negative subscale score (ρ=0.76) but weak correlations with the PANSS positive subscale (ρ=0.21) and Calgary Depression Rating Scale for schizophrenia (CDSS) total score (ρ=0.27).[30, level III]

Besides the above assessments, the self-administered WHO Disability Assessment Schedule II (WHODAS 2.0) has been used for assessing health status and disability in people with schizophrenia and mentally ill patients.[31, level III]

Assessment of people with possible schizophrenia consists of thorough history taking (collaborative history from patient/family/caregiver), physical examination, mental state examination (MSE) and investigations where indicated. This is summarised in **Table 1**.

Table 1. Initial Psychiatric Assessment

History taking	
History of present illness	Reason for current visit
	Current symptom
	Precipitating factor
Past psychiatric history	Hospitalisation and emergency visit for psychiatric issues including substances abuse
	Psychiatric treatment including type and duration, treatment setting, dose of medication and, response and adherence to treatment
	Prior psychiatric diagnosis and symptom including hallucination, delusion, negative symptom, aggressive idea or behaviour, suicidal idea or attempt, impulsivity
Substance use history	Tobacco, alcohol or illicit substance
	Recent or current substance use
Medical history	Allergy or drug sensitivity
	All current medication use and side effect including non-prescribed medication or supplement
	Current or past medical/surgical illness including related hospitalisation e.g. • endocrine disease e. g. diabetes mellitus, thyroid disorder • cardiovascular disease e.g. hypertension • dyslipidemia • neurological disease • connective tissue disease e.g. systemic lupus erythematosus • infectious disease e.g. human immunodeficiency virus, tuberculosis, sexually transmitted infections • malignancy • physical trauma or head injury
	Traditional and complementary medicine

Family history	History of mental illness including history of suicidal or aggressive behaviour
Social history	Presence of psychosocial stressors e.g. financial, housing, legal, school/occupation, interpersonal relationship, social support, disfiguring or terminal illness
	Exposure to physical, sexual or emotional trauma or childhood abuse
Pre-morbid personality	Temperament, stress management, interest or hobby, relationship, beliefs and personality traits. These include highest and current level of functioning/education/ vocation, interpersonal relationships and independent living
Physical examination	Full physical examination including height, weight and body mass index (BMI), vital signs, cardiovascular and neurological examinations
MSE	
Appearance and behaviour	• Level of consciousness • General appearance - body build, posture, cleanliness, dressing, evidence of weight loss, self-harm • Face - eye contact, emotional expression • Posture and movement - posture of depressed or anxious person, agitated, restless, biting nails etc. • Motor - fast or slow movement, choreoathetosis, tardive dyskinesia, dystonias, abnormal movement (e.g. grimacing, echopraxia, tics, mannerism/ stereotyped movement) • Attitude to examination and social behaviour - friendly, hostile, suspicious
Speech	• Production - spontaneity, speed (pressured or retarded), loudness, quantity, tone, quality (dysarthria) • Forms - neologism, punning and clang associations, expressive dysphasia • Content - obscene words, poor fluency (shyness, poor education, thought disorder or circumstantiality, receptive dysphasia, echolalia, perseveration), coherence, relevance
Mood and affect	• Mood (by asking the patient about predominant mood or subjective mood) - euthymic, depressed, elevated • Affect (by observation of the expression or objective mood) - types (anxious, sad, happy, angry, euphoria, elation), range (broad, restricted, blunted, flat), stability/lability (labile, non-labile), appropriateness/ congruity (congruent/incongruent)

Thought disturbances	Abnormal thought content - delusional, non-delusional a. Delusion • primary delusion (delusional mood, delusional perception, autochthonous delusion) • possession of thought (thought withdrawal, insertion, broadcast) • passivity phenomena (experience of action, thought, feeling under control) • theme/content (persecutory, grandiose, nihilistic, somatic) • secondary delusion (mood congruence/ incongruence) b. Non-delusional • phobia, obsession, suicidal ideation Abnormal thought form • fluency (circumstantiality, loosening of associations) • flow (pressured, poverty of thought, thought blocking, perseveration, derailment, tangential, flight of idea) • word (punning, neologism) Suicidal thought Homicidal thought
Perceptual disturbance	• Hallucination - auditory, visual, olfactory, gustatory, tactile • Illusion • Pseudo-hallucination • Depersonalisation, derealisation
Cognitive function	Orientation/memory/attention and concentration/abstract thinking/general knowledge
Judgement	Patient's recognition of consequences of action
Insight	Patient's awareness and understanding of illness and need for treatment

Adapted from: Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry. 2020:1;177(9):868-872.

To date, there is no evidence found on biological assessment for schizophrenia. Nevertheless, relevant investigations should be performed if a medical condition is suspected.

3.2 Criteria of Diagnostic Classifications

The diagnosis and classification of schizophrenia is important and based on Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) or International Classification of Diseases and Related Health Problem 10th Revision (ICD-10). Refer to **Appendix 3** on **Diagnostic Criteria for Schizophrenia:(DSM-5)** and **Appendix 4** on **International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD 10).**

The ICD-11 was released on June 18, 2018 and was officially presented at the World Health Assembly in May 25, 2019. It will be used as the official reporting system by member states on January 1, 2022.

Issues arise on the sufficiency of current ICD-10 or DSM-5 on therapeutic and prognostic management of schizophrenia. The stability of the diagnostic criteria are as below.

- A large randomised controlled trial (RCT) on second-generation antipsychotic (SGA) in acute schizophrenia showed 99.5% of the patients with DSM-IV met DSM-5 diagnostic criteria for schizophrenia.[32, level I]
- In a small prevalence study on individuals with DSM-IV schizophrenia, DSM-5 changes in criteria A showed a negligible effect on the prevalence of schizophrenia as over 98% of individuals continued to receive a DSM-5 diagnosis of schizophrenia.[33, level III]
- A meta-analysis of 42 studies showed a high diagnostic stability in schizophrenia spectrum using either DSM-IV or ICD-10.[34, level II-2]

In a Cochrane systematic review of 21 studies of old and limited qualities, first rank symptoms correctly identified schizophrenia 75% to 95% of the time.[35, level III]

- Disease severity is assessed based on presenting psychopathology and risk assessment (risk to self and/or others). The psychopathology may be assessed using the severity scale e.g. PANSS or BPRS by trained personnel.

Recommendation 2

- People with possible schizophrenia should be assessed thoroughly by history taking (self-report and collateral), physical examination, mental state examination and relevant investigations (if indicated).
- Schizophrenia should be diagnosed using either Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) or International Classification of Diseases and Related Health Problem 10th Revision (ICD-10).

4. TREATMENT

The modalities of treatment in schizophrenia are:

- pharmacological intervention
- physical intervention
- psychosocial intervention
- service level intervention

These are offered both in acute and relapse prevention phases.

People with schizophrenia who present early and for the first time at primary care should be provided with the following:[17]

- assessment and early treatment
- early referral to specialist care in the following circumstances (refer to **Subchapter 2.3**)
- initial treatment and urgent referral in the acutely-ill cases
- collaboration with hospital-based psychiatric services
- registration of cases at health clinics and the National Mental Health Registry

- Current available guidelines for mental health services in primary care:
  - *Garispanduan Perkhidmatan Rawatan Susulan Pesakit Mental di Klinik Kesihatan 2009*
  - *Garispanduan Pelaksanaan Perkhidmatan Pemulihan Psikososial Bagi Pesakit Mental Di Penjagaan Kesihatan Primer 2000*

4.1 Pharmacological Intervention

Antipsychotics (APs) treat the symptoms of schizophrenia. Since the discovery of chlorpromazine in 1952, APs remain the cornerstone of schizophrenia treatment in both acute as well as maintenance phases. They generally can be classified as first-generation APs (FGA) and second-generation APs (SGA). The FGAs derive their effect on positive symptoms by predominantly blocking the dopamine 2 (D2) receptors, which often results in debilitating extrapyramidal side effects (EPS). The SGAs are however more versatile and act by blocking other subtype dopamine receptors (e.g. clozapine blocks D1 and D4) as well as serotonergic, adrenergic and histaminergic receptors. SGAs tend to cause more metabolic issues.

Although there may be meaningful distinctions in clinical response and tolerability of different APs in an individual patient, there is no definitive evidence that one AP is superior to another, with the possible exception of clozapine.

It is essential for clinicians to discuss with the patients on the best possible medication for them in terms of both effectiveness and tolerability and, develop a dosing regimen that will minimise the impact of side effects on daily functions. Their previous experiences with medication should also be considered. An evidence-based ranking of FGAs and SGAs or an algorithmic approach to AP selection is not possible because of the significant heterogeneity in clinical trial designs and, limited numbers of head-to-head comparisons of APs and clinical trial data for a number of APs.[36]

The APs registered in Malaysia, either in oral, intramuscular (IM) or long-acting injectable (LAI) depot IM preparations in alphabetical orders are listed below:

FGAs	SGAs
• Chlorpromazine • Flupenthixol • Fluphenazine • Haloperidol • Perphenazine • Sulpiride • Trifluoperazine • Zuclopenthixol	• Amisulpride • Aripiprazole • Asenapine • Brexpiprazole • Cariprazine • Clozapine • Olanzapine • Paliperidone • Quetiapine • Risperidone • Ziprasidone

In the treatment of acute phase of schizophrenia, the recommended optimal oral dose of AP is two or three times minimum effective dose (MED) [(RR for 2-fold MED is 1.24 (95% CI 1.00 to 1.54) and for 3-fold MED is 1.44 (95% CI 1.10 to 1.89)] and adverse effects (AEs) should be closely monitored.[37, level I] In relapse prevention, the standard doses should be used.[17] APs should be used for at least 6 - 8 weeks with adequate dosage before switching to other APs.[38, level III] The CPG DG opines that 2 - 6 weeks duration of APs should be used to assess response in schizophrenia.

Refer to:

i. **Appendix 5 (Dosing Regimen for Oral Antipsychotics)** and **Appendix 6 (Dosing Regimen for Depot Injections of Antipsychotics)**
ii. **Table 2 (Relative AEs of APs)** and **Table 3 (Common AEs of APs and their management strategies)**
iii. **Appendix 8** on **Monitoring Parameters for Antipsychotics**

4.1.1 Pharmacological agents

In a meta-analysis of 20 RCTs on people with schizophrenia with follow-up from 5 to 14 years, those on any APs had lower mortality risk

compared with those without the treatment (RR=0.57, 95% CI 0.46 to 0.76). Causes of death reported were cardiovascular disease in 15.7% and suicide in 6.7%. The remaining causes were described as other natural, unnatural or undetermined. However, reasons for the increased risk of death for those without APs requires further research. Quality of the primary studies was variable but most scored as moderate.[39, level I]

A network meta-analysis on schizophrenia showed that APs reduced overall symptoms compared with placebo, with SMD ranging from -0.89 (95% CrI -1.08 to -0.71) for clozapine to -0.03 (95% CrI -0.59 to 0.52) for levomepromazine. The effectiveness differences between APs were mostly small. Only clozapine, amisulpride, zotepine, olanzapine and risperidone were significantly more effective for the primary outcome (change in overall symptoms) than other APs. With regard to side effects:[40, level I]

- the RR for sedation ranged from 0.92 (95% CrI 0.17 to 2.03) for pimozide to 10.20 (95% CrI 4.72 to 29.41) for zuclopenthixol
- the MD for weight gain ranged from -0.16 kg (-0.73 to 0.40) for ziprasidone to 3.21 kg (2.10 to 4.31) for zotepine
- the MD for prolactin elevation ranged from -77.05 ng/mL (-120.23 to -33.54) for clozapine to 48.51 ng/mL (43.52 to 53.51) for paliperidone
- the MD for QTc prolongation ranged from -2.21 ms (-4.54 to 0.15) for lurasidone to 23.90 ms (20.56 to 27.33) for sertindole

In addition, the RR on the use of antiparkinsonian medication as a measure of EPS ranged from 0.46 (0.19 to 0.88) for clozapine to 6.14 (4.81 to 6.55) for pimozide. The certainty of the evidence in this network meta-analysis was generally low.

In a Cochrane systematic review, AP combination may improve clinical response compared with AP monotherapy in schizophrenia (RR=0.73, 95% CI 0.64 to 0.83). There was no significant difference in relapse (RR=0.63, 95% CI 0.31 to 1.29) and rate of hospitalisation (RR=0.96, 95% CI 0.36 to 2.55). There was also no significant difference for serious AEs, movement disorders and weight gain. Most evidence was from short-term trials and graded very low in quality.[41, level I]

In a network meta-analysis of 19 RCTs on acute treatment in first episode of schizophrenia:[42, level I]

- for overall reduction of symptoms, amisulpride (SMD= -0.37, 95% CI -0.61 to -0.14), olanzapine (SMD= -0.25, 95% CI -0.39 to -0.12), ziprasidone (SMD= -0.25, 95% CI -0.48 to -0.01) and risperidone (SMD= -0.14, 95% CI -0.27 to -0.01) were more effective than haloperidol
- in improvement of negative symptoms, olanzapine was more effective than risperidone (SMD= 0.20, 95% CI 0.03 to 0.37) and haloperidol (SMD= 0.31, 95% CI 0.13 to 0.48)

- in treatment of parkinsonism,
  - olanzapine showed less frequent use of drugs compared with haloperidol (OR=0.10, 95% CI 0.03 to 0.29), zuclopenthixol (OR=0.02, 95% CI 0.00 to 0.37) and risperidone (OR=0.24, 95% CI 0.07 to 0.78)
  - quetiapine showed less frequent use of drugs compared with haloperidol (OR=0.10, 95% CI 0.01 to 0.75) and zuclopenthixol (OR=0.02, 95% CI 0.00 to 0.66)
- haloperidol showed less weight gain compared with olanzapine (SMD=0.63, 95% CI 0.11 to 1.16)

The primary evidence was of very low to moderate quality.

There was no RCT found on the use of depot AP on first episode of schizophrenia.

- APs are the mainstay of pharmacological treatment in schizophrenia.
- There is small difference in effectiveness between APs except for clozapine.
- All APs are different in their side effects profiles.
- Reasons to switch include lack of clinical response, intolerability and drug interaction.
- The choice of APs mainly depends on their differences in side-effect profiles.
- APs should be used for 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 years.
- There is limited evidence in using combination APs.

Recommendation 3
- Antipsychotics should be offered in schizophrenia as it is the mainstay of the treatment.

4.1.2 Rapid tranquillisation in acute exacerbation

In rapid tranquillisation, medications are used to calm the patient and not to induce sleep, so that he/she can be more accurately assessed by healthcare providers when stable. The medications commonly used are FGA, SGA and benzodiazepines. Side effects should be anticipated and antidotes should be readily available. The choice of medication depends on the underlying cause of the aggression.[43]

Parenteral [intramuscular (IM) or intravenous (IV)] medications are used during acute exacerbation of schizophrenia to stabilise the aggressiveness of the patients. Evidence supporting the effectiveness and safety of this clinical practice is as follows:

- A meta-analysis of 167 RCTs showed that APs were more effective than placebo in reducing positive symptoms (SMD=0.45, 95% CI 0.40 to 0.50) and negative symptoms (SMD=0.35, 95% CI 0.31 to 0.40). However, they had more movement disorders (RR=1.93, 95% CI 1.65 to 2.29), sedation (RR=2.80, 95% CI 2.30 to 3.55) and weight gain (SMD= -0.40, 95% CI -0.47 to -0.33).[44, level I]
- In a Cochrane systematic review, IM aripiprazole:[45, level I]
  - prevented the need of additional injection to achieve tranquilisation by 31% compared with placebo at 24 hours (RR=0.69, 95% CI 0.56 to 0.85); in addition, it was more effective in reducing agitation in two hours (RR=1.50, 95% CI 1.17 to 1.92)
  - showed no difference with IM haloperidol in the need of additional injection to achieve tranquilisation and reducing agitation in two hours
  - was less effective in reducing agitation in two hours compared with IM olanzapine (RR=0.77, 95% CI 0.60 to 0.99)
  - showed no difference in adverse effects with placebo, IM haloperidol and IM olanzapine

  The primary evidence was of very low quality. IM olanzapine is not available in Malaysia.
- In another Cochrane systematic review, IM haloperidol compared with placebo:[46, level I]
  - prevented non-tranquillisation by 12% at two hours (RR=0.88, 95% CI 0.82 to 0.95)
  - reduced the need of repeated injection by 49% at 24 hours (RR=0.51, 95% CI 0.42 to 0.62)
  - was more effective in reducing agitation in two hours (RR=1.62, 95% CI 1.28 to 2.07)
  - had more overall adverse events at 72 hours (RR=1.78, 95% CI 1.23 to 2.59)

  The primary papers were mainly on schizophrenia and of very low quality.
- In an RCT, oral haloperidol 15 mg, olanzapine 20 mg and risperidone 2 - 6 mg improved PANSS psychotic agitation subscale score significantly as early as two hours from baseline and sustained until day five in acute severe psychotic agitation in schizophrenia. However there was no difference between the three medications.[47, level I]
- NICE recommends IM haloperidol combined with promethazine for rapid tranquillisation in adults.[22]
- In the previous MoH CPG, IM preparations recommended for rapid tranquillisation are lorazepam, midazolam, haloperidol, olanzapine, ziprasidone and zuclopenthixol acetate. Wherever possible, a single agent is preferred. When rapid tranquillisation is urgently needed, a combination of IM haloperidol plus lorazepam or promethazine should be considered.[17]

- If patient is cooperative, oral medications e.g. olanzapine or risperidone is preferred.
- If patient is uncooperative, parenteral medications e.g. IM haloperidol and IM midazolam or IV diazepam can be used.

4.1.3 Depot/long-acting injectable antipsychotics in achieving remission

Treatment adherence is a widely recognised problem in schizophrenia but knowledge on improving it is still limited. About 50 - 70% of people with schizophrenia had treatment non-adherence which includes failure to enter a treatment programme, default outpatient clinic appointments and incomplete implementation of instructions (including prescriptions).[17; 22] Clinically effective management will result in low non-adherence rate. Studies have shown that non-adherence in psychiatric patients resulted in high morbidity and mortality.

In a prospective cohort study, clinic defaulters had lower social functioning and more severe mental disorder e.g. schizophrenia than those who attended the clinic. Patients who missed their appointment more than 12 months were more likely to have been admitted than clinic attendees.[48, level II-2]

Depot or LAI APs may be considered based on patient's preference or when there is medication adherence issue for maintenance treatment in schizophrenia.[22; 36; 49] Available such preparations in Malaysia are:

- fluphenazine decanoate
- flupenthixol decanoate
- zuclopenthixol decanoate
- risperidone microspheres
- paliperidone palmitate
- aripiprazole

A meta-analysis of five RCTs showed that depot AAPs had higher remission rate than oral AAPs for follow-up lasting ≥1 year (RR=1.42, 95% CI 1.18 to 1.71). However, extrapyramidal symptoms (RR=1.61, 95% CI 1.27 to 2.04) and prolactin-related adverse effects (RR=2.48, 95% CI 1.60 to 3.84) occurred more frequently in the depot preparation.[50, level I] The primary evidence was of moderate to high quality.

A cross-sectional study showed that 17.6% of psychiatrists had initiated depot APs for people with schizophrenia having non-adherence issues. The initiation was significantly and positively associated with public insurance, prior inpatient admission, longer duration of non-adherence, average or above average intellectual functioning and living in a mental health residence. The use of depot was inversely associated with

SGA and other oral psychotropic medications prior to medication non-adherence.[51, level III]

Recommendation 4
- Treatment adherence should be regularly monitored and maximised until the termination of treatment is indicated in schizophrenia.
- Long-acting (depot) injectable antipsychotic in schizophrenia:
  - should be offered when there is medication adherence issue
  - may be considered based on patient's preference

4.1.4 Antipsychotics in relapse prevention

In a large Cochrane systematic review of 75 RCTs, APs were better than placebo in preventing relapse in schizophrenia at 12 months (RR=0.38, 95% CI 0.32 to 0.45; NNTB=3). Furthermore, they also:[52, level I]
- reduced hospitalisation (RR=0.43 95% CI 0.32 to 0.57; NNTB=8)
- lessen aggressive behaviour (RR=0.35, 95% CI 0.19 to 0.66; NNTB=50)
- improved quality of life (QoL) (SMD= -0.32, 95% CI -0.57 to -0.07)

However, they increased movement disorders (RR=1.52, 95% CI 1.25 to 1.85; NNTH=20), sedation (RR=1.52, 95% CI 1.24 to 1.86) and weight gain (RR=1.69, 95% CI 1.21 to 2.35; NNTH=25). The evidence for relapse prevention and hospitalisation were of high quality.

A meta-analysis showed that SGA was more effective than FGA in preventing relapse in schizophrenia (RR=0.80, 95% CI 0.70 to 0.91; NNT=17).[53, level I] There was no quality assessment of primary paper mentioned. However, in the recent Cochrane systematic review, subgroup analysis found no significant difference in reduction of relapse risk in schizophrenia between FGA (RR=0.35, 95% CI 0.25 to 0.48) and SGA (RR=0.39, 95% CI 0.32 to 0.48).[52, level I]

In a network meta-analysis on schizophrenia, olanzapine was more effective than chlorpromazine (OR=0.35, 95% CI 0.14 to 0.88) and haloperidol (OR=0.50, 95% CI 0.30 to 0.82) in reducing relapses. The primary papers were of moderate quality.[54, level I]

In another meta-analysis, studies before 1991 which were exclusively on long-acting injection (LAI) fluphenazine showed that the medication was more effective in preventing relapse compared with oral FGA in schizophrenia (RR=0.79, 95% CI 0.65 to 0.96). There was no difference in effectiveness between SGA LAI and oral SGA.[55, level I] However, there was no quality assessment of primary paper mentioned. Depot preparations may be considered when treatment adherence issue arises.[17]

A large meta-analysis of 24 RCTs compared the effectiveness and safety of standard vs reduced dose of APs. The median duration of follow-up was 52 weeks (IQR 46 - 53). Doses were classified as:[56, level I]

- standard dose (above or equal to the lower limit of the recommended target dose range for acute treatment)
- low dose (50 - 99% of the lower limit)
- very low dose (<50% of the lower limit)

Compared with standard dose:

- low dose increased risk of relapse by 44% (RR=1.44, 95% CI 1.10 to 1.87) and all-cause discontinuation by 12% (RR=1.12, 95% CI 1.03 to 1.22)
- very low dose increased risk of relapse by 72% (RR=1.72, 95% CI 1.29 to 2.29) and all-cause discontinuation by 31% (RR=1.31, 95% CI 1.11 to 1.54)

In terms of safety, there were no significant differences between different doses in intolerability -related discontinuations, anticholinergic use and rating scale-based assessments of akathisia, dyskinesia and parkinsonism. Most primary studies in the meta-analysis were classified as having some concerns in risk of bias assessment.

Recommendation 5

- Antipsychotics (APs) should be offered to prevent relapse in schizophrenia.
  - Second-generation APs are the preferred choice.
  - Standard dose of APs should be considered as maintenance treatment.

4.1.5 Intermittent treatment in relapse prevention

In a Cochrane systematic review on people with schizophrenia, intermittent AP treatment compared with maintenance treatment at ≥26 weeks follow-up showed:[57, level I]

- higher relapse (RR=2.46, 95% CI 1.70 to 3.54)
- higher hospitalisation rate (RR=1.65, 95% CI 1.33 to 2.06)
- no difference in tardive dyskinesia (RR=1.15, 95% CI 0.58 to 2.30)

The quality of evidence in the first two outcomes was moderate while the last outcome low.

In a later meta-analysis of ten studies, stabilised people with schizophrenia who had been exposed for at least six months to intermittent or placebo strategies had higher risk of relapse compared with those on continuous treatment with OR of (3.36, 95% CI 2.36 to 5.45) and 5.64 (95% CI 4.47 to 7.11) respectively.[58, level I]

Recommendation 6

- Intermittent treatment using antipsychotics should be avoided in schizophrenia.

4.1.6 Treatment for extrapyramidal signs, sedation and weight gain associated with antipsychotics

There are several common adverse effects of APs e.g. sedation, EPS, weight gain, constipation, cardiovascular complications and metabolic syndrome. These adverse effects can happen at any point of time and majority are dose dependent.

Summary of **Relative AEs of APs** and **Common AEs of APs with their management strategies** are shown in **Table 2** and **Table 3**.

- Neuroleptic malignant syndrome (NMS) is a rare medical emergency but potentially life-threatening condition caused by APs. It is characterised by fever, rigidity, tremors, sympathetic nervous system dysregulation and creatinine kinase elevation. Immediate diagnosis and treatment are essential and this condition should be referred to the medical team.

Table 2. Relative AEs of APs

APs	Constipation	Sedation	Weight gain	Akathisia	Parkinsonism	Tardive dyskinesia	Anticholi-nergic	Hypotension	QT prolongation	Prolactin elevation
Amisulpride	++	-	+	+	+	+	-	-	++	+++
Aripiprazole	+	-	-	+	-	+	-	-	+	-
Asenapine	+	+	+	+	-	+	-	-	+	+
Brexpiprazole	-	-	-	-	-	-	-	-	-	-
Cariprazine	++	-	-	+	-	-	-	-	-	-
Chlorproma-zine	++	+++	++	+	++	++	++	+++	++	+++
Clozapine	+++	+++	+++	-	-	-	+++	+++	-	-
Flupentixol	+	+	++	++	++	+	++	+	+	+++
Fluphenazine	+	+	+	++	+++	+	+	+	+	+++
Haloperidol	++	+	+	+++	+++	++	+	+	++	++
Olanzapine	++	++	+++	-	-	+	+	+	+	+
Paliperidone	++	+	++	+	+	+	+	++	+	+++
Perphenazine	+	+	+	++	+++	++	+	+	+	+++
Quetiapine	++	++	++	-	-	+	+	++	++	-
Risperidone	++	+	++	++	+	+	+	++	+	+++
Sertindole	-	-	+	+	-	+	-	+++	+++	-
Sulpiride	++	-	+	+	+	-	-	-	+	+++
Trifluoperazine	-	+	+	+	+++	+	+	+	-	+++
Ziprasidone	+	+	-	+	+	+	-	+	++	+
Zuclopenthixol	++	++	++	++	++		++	+	-	+++

+++ High incidence/severity
++ Moderate incidence/severity
+ Low incidence/severity
- Very low incidence/severity

Source:

1. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry (14th Edition). London: Wiley Blackwell; 2021
2. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018;17(3):341-35

Table 3. Common AEs of APs and their management strategies

Adverse effects	Onset	Dose dependent	Management strategies			Comments
			First choice	Second choice	Third choice	
Constipation	Within the first four months of AP administration	✓	• Ensure adequate fibre, fluid and exercise • Osmotic laxatives (e.g. lactulose)/ stimulant laxatives (e.g. senna)	Change to AP with lower risk (refer to **Table 2**)	-	• Clozapine-induced gastrointestinal hypomotility is a common AE, 3 times that seen with other APs • Avoid bulk-forming laxatives • Stop other medicines that may contribute to constipation if possible
EPS: Dystonia	Within hours to days of AP administration or dose increase	✓	Anticholinergic medication (e.g. trihexyphenidyl, procyclidine)	Antihistaminic medication (e.g. diphenhydramine)	Benzodiazepine (e.g. clonazepam, diazepam)	Where symptoms do not respond to simpler measures, including switching to an AP with low propensity for EPS, botulinum toxin may be effective
EPS: Pseudoparkinsonism (tremor, rigidity, bradykinesia)	Days to weeks after AP administration or dose increase	✓	Reduce dose of AP	Change to AP with lower risk (refer to **Table 2**)	Anticholinergic medication (e.g. trihexyphenidyl, benztropine)	• Majority of patients do not require long-term anticholinergic medication (its use should be reviewed at least every 3 months and not to be prescribed at night)
Akathisia	Within hours to weeks of AP administration or dose increase	✓	Reduce dose of AP	Change to AP with lower risk (refer to **Table 2**)	Beta-blockers (e.g. propranolol)	• 5-HT2 antagonists e.g. cyproheptadine, mirtazapine, trazodone, and mianserin may help • Antimuscarinic or benzodiazepine may also be useful • Anticholinergics are generally unhelpful

Adverse effects	Onset	Dose dependent	Management strategies			Comments
			First choice	Second choice	Third choice	
Tardive dyskinesia	After months to years of AP administration	✓	• Reduce dose of AP • Stop anticholinergic if prescribed	Change to AP with lower risk (refer to **Table 2**)	Valbenazine, tetrabenazine or deutetrabenazine (not available in Malaysia yet)	• Change to AP with lower propensity for TD e.g. clozapine and quetiapine
Sedation	Within hours to days of AP administration	✓	Dose at night before sleep	Reduce dose	Change to less sedating APs (refer to **Table 2**)	Stimulants have unclear benefit
Diabetes mellitus	Within one month of AP administration	✓	Change to AP with lower risk(haloperidol, aripiprazole, amisulpride, ziprasidone)	Treat accordingly and refer to Clinical Practice Guidelines Management of Type 2 Diabetes Mellitus (6th Edition)*		-
Weight gain	Within three months of AP administration	✓	Behavioural modification (diet, exercise)	Behavioural modification + change AP	Add aripiprazole/ cariprazine to existing treatment	Pharmacological medication e.g. metformin should be considered only where behavioural methods, switching of AP have failed or where obesity presents clear, immediate physical risk to the patient
Dyslipidaemia	Within three months of AP administration	✓	Behavioural modification (diet, exercise) + change AP	Treat accordingly and refer to local CPG on Management of Dyslipidaemia (5th Edition)**		Stimulants have unclear benefit
Hyperprolactinaemia	Within hours to months of AP administration	✓	Change to 'prolactin-sparing' APs (aripiprazole, quetiapine, clozapine)	Add aripiprazole	Consider dopamine agonists (cabergoline, bromocriptine, amantadine) or referral to endocrinologist	Metformin has been shown to improve prolactin related symptoms and levels respectively

Adverse effects	Onset	Dose dependent	Management strategies			Comments
			First choice	Second choice	Third choice	
Orthostatic hypotension	Within hours to days of AP administration or dose increase	✓	Adjust dose or slow dose titration	Adequate hydration	Change to AP with lower risk (refer to **Table 2**)	Avoid APs that are potent α 1-adrenergic receptor antagonist (clozapine, quetiapine) and/or concomitant intake of medications that can reduce BP
Electrocardiogram (ECG) changes - QT prolongation	After 2 - 4 weeks of AP administration	✓	• >440 ms (men)/ >470 ms (women) but <500 ms: reduce dose or switch AP with lower risk (refer to Table 2 below • >500 ms: ○ repeat ECG ○ stop suspected causative drugs and switch to lower risk AP ○ immediately refer to cardiologist Abnormal T-wave morphology: review treatment, consider reduce dose or switching to lower risk AP	-		Risk is high with any IV AP or combination of APs with doses exceeding recommended maximum

*Available at https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/CPG_T2DM_6th_Edition_2020_13042021.pdf

Adapted:

1. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry. 2020;7(1):64-77
2. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018;17(3):341-35
3. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry (13th Edition). London: Wiley Blackwell; 2018

4.2 Physical Intervention

4.2.1 Electroconvulsive therapy

Electroconvulsive therapy (ECT) may be a useful adjunct to AP when there is a need for rapid improvement and reduction of symptoms or limited response to AP in schizophrenia.[17; 36; 49; 59] ECT in combination with AP may be beneficial in people with treatment-resistant schizophrenia (refer to **Subchapter 7.1.3** on **Treatment for treatment-resistant schizophrenia**)

4.2.2 Transcranial magnetic stimulation

In a Cochrane SR of 41 RCTs on schizophrenia or schizoaffective/related disorder, temporoparietal transcranial magnetic stimulation (TMS) compared with sham TMS or others showed:[60, level I]

- improved global state on CGI scale (MD= -0.5, 95% CI -0.76 to -0.23)
- positive symptoms on PANSS scale (MD= -6.09, 95% CI -10.95 to -1.22)

However, study subjects showed no significant clinical improvement in global state or early withdrawal from study when TMS was used as adjunctive therapy.

4.2.3 Transcranial direct current stimulation

A meta-analysis of 10 RCTs found no effect of transcranial direct current stimulation compared with sham treatment on auditory hallucinations, positive symptoms or negative symptoms in schizophrenia or schizoaffective disorder.[61, level I]

Recommendation 7

- Electroconvulsive therapy may be considered in schizophrenia to achieve rapid and short-term improvement of severe symptoms after an adequate trial of antipsychotic is proven ineffective and in treatment-resistant schizophrenia.

4.3 Psychosocial Intervention

There are various forms of psychosocial intervention which are not limited to psychotherapy and psychological techniques in the management of people with schizophrenia. The aim of these psychosocial intervention varies depending on the treatment goal. The commonly used interventions are discussed below.

4.3.1 Psychoeducation

Psychoeducation improves understanding of mental health issues, recognising early warning signs of relapse and understanding on the work of psychiatric services.[22] A psychoeducation programme includes key information about diagnosis, symptoms, psychosocial

interventions, medications and side effects as well as information about stress and coping, crisis plans, early warning signs (EWS) and, suicide and relapse prevention.[36]

In a Cochrane systematic review of low-quality evidence on people with schizophrenia, brief psychoeducation either individual, group or family, was better than routine care in prevention of:[62, level I]

- non-compliance with medication at short-term (RR=0.63, 95% CI 0.41 to 0.96) and medium-term (RR=0.17, 95% CI 0.05 to 0.54)
- relapse at medium-term (RR=0.70, 95% CI 0.52 to 0.93)

Another Cochrane systematic review on promoting well-being and reducing distress of siblings of people with schizophrenia, psychoeducation was better than standard care in coping with (family) burden at 12 months (MD= -8.80, 95% CI -15.22 to -2.34).[63, level I]

In an RCT looking on community-based comprehensive intervention which included psychoeducation, social skills training, cognitive behaviour therapy (CBT) and, strategies against stigma and discrimination (SASD) vs control for people with schizophrenia, the intervention was significantly effective at nine months on the following outcomes:[64, level I]

- overcoming stigma
- anticipated discrimination
- functioning based on GAF total score
- reduction in BPRS total score
- reduction in PANSS negative score

EWS are early symptoms that are distinctive to the person with schizophrenia and often precede acute psychotic relapse. Examples are change in sleep pattern, irritability, social withdrawal, difficulty in concentration and decline in self-care. Thus, intervention on EWS aims to detect and manage these signs for prevention of relapse. A Cochrane systematic review showed that training to recognise EWS of relapse in schizophrenia was better compared with treatment as usual in:[65, level I]

- preventing relapses (RR=0.53, 95% CI 0.36 to 0.79)
- preventing re-hospitalisation (RR=0.48, 95% CI 0.35 to 0.66)
- improving medication compliance (MD=0.57, 95% CI 0.42 to 0.77)

In subgroup analysis, time taken to relapse after treatment was longer if EWS intervention was delivered to patients only compared with treatment as usual (HR=0.26, 95% CI 0.13 to 0.53), but no difference was shown when EWS intervention was delivered to both patient and their carer/health professionals. Apart from that, time to re-hospitalisation after treatment was longer (HR=0.62, 95% CI 0.46 to 0.83) when the intervention was delivered to both patients and their carer/health professional. In this review, the overall quality of the 34 RCTs was very low.

SIGN recommends that psychoeducation should not be offered as a stand-alone intervention to people with schizophrenia and professionals should ensure that people with schizophrenia and their families/carers are informed about the illness.[49] APA recommends that people with schizophrenia receive psychoeducation.[36]

In Malaysia, family psychoeducation programmes have been conducted for many years based on the Family Link programme module.[66]

Recommendation 8
- Psychoeducation which includes early warning signs interventions should be given in addition to other interventions in schizophrenia.

4.3.2 Supported employment

In a Cochrane systematic review for adults with severe mental illness where schizophrenia disorders were well represented, supported employment increased levels of any employment compared with other vocational approaches (RR=3.24, 95% CI 2.17 to 4.82). It also showed some advantages in other secondary outcomes e.g. duration of any form of paid employment, job tenure for competitive employment and time to first competitive employment in long-term. However the primary papers were of very low quality.[67, level I]

NICE recommends to offer supported employment programmes to people with psychosis or schizophrenia who wish to find or return to work. Apart from that, it is recommended to consider other occupational or educational activities, including pre-vocational training, for people who are unable to work or unsuccessful in finding employment.[22]

APA also recommends that patients with schizophrenia receive supported employment services.[36] Guidelines on implementation of supported employment programme for people with mental illness including schizophrenia has also been developed locally.[17]

Recommendation 9
- Supported employment should be offered in schizophrenia.

4.3.3 Cognitive remediation therapy

Cognitive impairment is a core feature of schizophrenia that is fully evident at the time of first episode and the most affected areas are attention, verbal memory and executive functioning. Cognitive deficits in schizophrenia influence functional outcomes in work, independent living, social functioning and illness management. Cognitive remediation therapy (CRT) is a behavioural treatment intervention that aims to

improve the cognitive processes e.g. memory, attention, executive function, metacognition and social cognition. It uses techniques which modify cognition in people with schizophrenia e.g. errorless learning, repetition and positive reinforcement.[68]

A meta- analysis of 38 moderate quality RCTs demonstrated a moderate effect of CRT on global cognition in people with schizophrenia (Cohen's d=0.45, 95% CI 0.31 to 0.59). The CRT also showed significant effect on all cognitive domains i.e. attention/vigilance (Cohen's d=0.25), processing speed (Cohen's d=0.258), verbal working memory (Cohen's d=0.346), verbal learning and memory (Cohen's d=0.410), reasoning/ problem solving (Cohen's d=0.572) and social cognition (Cohen's d=0.651).[69, level I]

The meta-analysis also suggested that functioning outcomes were best achieved by adding cognitive remediation to other rehabilitation programmes. The cognitive remediation programmes on psychosocial functioning reported significant stronger effects in studies that provided adjunctive psychiatric rehabilitation (Cohen's d=0.59, 95% CI 0.30 to 0.88) compared with those on cognitive remediation alone (Cohen's d=0.28, 95% CI -0.02 to 0.58).[69, level I]

CRT has been suggested for people with schizophrenia.[36] It may be offered as part of a multimodal psychosocial intervention.[17] in people with schizophrenia with persisting problems associated with cognitive difficulties.[49]

Recommendation 10

- Cognitive remediation therapy may be considered as an intervention for cognitive difficulties in schizophrenia.

4.3.4 Social skills training

Social skills training (SST) is a psychosocial intervention, whether group or individual, aimed at enhancing the social performance and reducing the distress and difficulty in social situations. A Cochrane systematic review of 13 studies found that in people with schizophrenia, compared with standard care, SST:[70, level I]

- significantly improved social functioning based on various rating scales
- significantly improved mental state based on various severity rating scales
- prevented relapse (RR=0.52, 95% CI 0.34 to 0.79)

The primary papers were of very low quality.

Existing evidence-based guidelines do not strongly recommend SST in the management of schizophrenia.[22; 36; 49]

Recommendation 11
- Social skills training may be offered in schizophrenia.

4.3.5 Peer support services

Peer support is a social emotional support which is mutually provided by persons having a mental health condition to others sharing a similar problem in order to bring about a desired social or personal change.[22]

A Cochrane systematic review found very limited and very low quality of evidence on the effectiveness of peer support for people with schizophrenia. In view of that, it could not be recommended as yet.[71, level I]

NICE recommends to consider peer support for people with schizophrenia to improve their experience and quality of life. It should be delivered by a trained peer support worker who has recovered from schizophrenia and remains stable. The workers should receive support from their whole team and, support and mentorship from experienced peer workers.[22]

Recommendation 12
- Peer support may be offered in schizophrenia.

4.3.6 Family therapy

Family therapy is a form of psychotherapy involving significant family members together with the person with schizophrenia based on individual family needs. It focuses on relationship in which the problem is manifested by providing support, skills and education through solution-oriented approach. It aims to reduce level of distress and improve communication within families.[49]

In a Cochrane systematic review of 53 studies on schizophrenia, family therapy:[72, level I]

- decreased frequency of relapse at 7 to 12 months (RR=0.55, 95% CI 0.48 to 0.62; NNT=7, 95% CI 6 to 8)
- reduced hospital admission at 7 to 12 months (RR=0.78, 95% CI 0.63 to 0.98; NNT 8 CI 6 to 13)
- improved non-compliance with medication (RR=0.60, 95% CI 0.49 to 0.73; NNT 6 CI 5 to 9)

The primary papers in the review were of poor methodological quality.

Recommendation 13
- Family therapy may be offered in schizophrenia.

4.3.7 Cognitive behaviour therapy

Cognitive behaviour therapy (CBT) is a structured, short-term, present-oriented psychotherapy. It focuses on problem solving and modifying dysfunctional thinking and behaviour. The application of CBT is based on conceptualisation of individual person's belief, behaviour and emotional experience.

Two meta-analyses on CBT against two different comparisons (other psychosocial intervention and standard care) showed:

- favourable outcomes in relapse, mental state, hospitalisation, social functioning and QoL in CBT added to standard care compared with standard care alone at long-term although non-significant in a Cochrane systematic review of 60 RCTs. However, the risk of adverse event was reduced in the combined treatment (CBT plus standard care) (RR=0.44, 95% CI 0.27 to 0.72). The quality of primary papers included was low.[73, level I]
- no significant difference between combination of CBT and standard care vs standard care and other psychosocial therapies in relapse, mental state, hospitalisation, adverse event, social functioning and QoL in another Cochrane systematic review. The quality of primary papers included was low.[74, level I]

CBT for psychosis (CBT-p) aims to normalise and make sense of the individual's psychotic experiences and also reduce the associated distress and impact on functioning. In a meta-analysis, CBT-p comparing with treatment as usual (TAU), CBT-p showed:[75, level I]

- improved functioning at the end-point of intervention (Hedges's g=0.25, 95% CI 0.14 to 0.33) but not sustained at follow-up (Hedges's g=0.10, 95% CI -0.07 to 0.26)
- reduced distress (Hedges's g=0.37, 95% CI 0.05 to 0.69)
- did not improve QoL (Hedges's g=0.04, 95% CI -0.12 to 0.19)

However, there was no report on quality of primary papers included in this study.

An RCT comparing Recovery-Oriented Cognitive Therapy (CT-R) with TAU showed that CT-R had earlier improvement in global functioning for people with low functioning schizophrenia with shorter duration of illness ≤12 years (Cohen's d 0.53).[76, level I]

Guidelines recommend CBTp in schizophrenia with persistent positive symptoms and/or depression.[17; 36; 49]

Recommendation 14

- Cognitive behaviour therapy for psychosis may be offered in schizophrenia.

4.3.8 Supportive psychotherapy/Counselling

Supportive psychotherapy/counselling relies on therapeutic alliances with the aim to assist change in attitude and behaviour and, reinforce the ability to cope.

A Cochrane systematic review of 24 very low quality RCTs found no significant differences in the relapse, hospitalisation and general functioning between supportive therapy and standard care in schizophrenia on medium- and/or long-term follow-up. However, supportive therapy had poorer outcomes compared with other psychological or psychosocial treatments at long-term follow-up:[77, level I]

- increased hospitalisation rates (RR=1.82, 95% CI 1.11 to 2.99)
- no clinical improvement in mental state (RR=1.27, 95% CI 1.04 to 1.54)
- dissatisfaction of treatment for the recipient of care (RR=3.19, 95% CI 1.01 to 10.7)

- Supportive psychotherapy has not been shown to be beneficial in the treatment of schizophrenia.

4.3.9 Others

- **Life skills training**

Life skills programmes for serious mental illness are rehabilitation programmes that address the needs associated with independent functioning e.g. financial awareness, communication, domestic care, personal self-care and community living skills.

A Cochrane systematic review found no good evidence to suggest that life skills programmes were effective for people with chronic mental illnesses which were mostly schizophrenia.[78, level I]

- **Exercise therapy**

A Cochrane systematic review of small RCTs looked into the effectiveness of exercise therapy on people with schizophrenia. The therapy was defined as any intervention either used alone or in conjunction with others where physical activity or exercise was considered to be the main or active element. Compared with standard treatment, exercise therapy improved depression, anxiety, both negative and positive PANSS scores and also physical fitness. However, it was less effective than yoga in total and negative PANSS scores.[79, level I]

- **Dance therapy**

Dance therapy uses movement and dance to explore a person's emotion in a non-verbal way by interpreting their dance to personal feelings.

In a Cochrane systematic review on schizophrenia, a moderate quality RCT showed that dance therapy was more effective than standard care in reducing PANSS negative symptoms score by 20 - 40% (RR=0.62, 95% CI 0.39 to 0.97).[80, level I]

- **Music therapy**

Music therapy is a systematic process of intervention promoting health using expression of music.

A Cochrane systematic review on schizophrenia, compared with standard care, showed that music therapy improved:[81, level I]

- global state at medium-term (NNTB=2, 95% CI 2 to 4)
- general mental state on PANSS at medium-term (SMD= -0.97 95% CI -1.31 to -0.63)
- negative symptoms on SANS at short-term (SMD= -0.5 95% CI -0.73 to -0.27) and medium-term (SMD= -0.55 95% CI -0.87 to -0.24)
- social functioning on Social Disability Screening Schedule (SDSS) at medium-term (SMD= -0.72, 95% CI -1.04 to -0.40)

The quality of primary papers used in the review was low to moderate.

- **Religion/spiritual activities**

Religious/spiritual activities are multidimensional approaches that promote positive coping. It provides sense of meaning and purpose, emotional comfort, personal control and connection with others and a higher power.

In a small cross-sectional study on schizophrenia, there was a modest correlation between positive religious coping and psychological aspect in QoL (r=0.28, p=0.03).[82, level III]

5. SERVICE LEVEL INTERVENTION

Following the global paradigm shifts from institutionalisation to community-based mental health services, Malaysia is steadily progressing towards developing more community-based psychiatric services. Hence this chapter addresses this issue based on common service level interventions provided in the management of schizophrenia.

5.1 Crisis and Emergency Service

Crisis and Emergency Mental Health Service provides intensive care in the community for people with acute psychiatric symptoms, thus avoiding the need for hospitalisation. A Cochrane systematic review of mixed quality RCTs on mainly schizophrenia showed that those receiving crisis intervention services compared with standard care had:[83, level I]

- fewer re-admissions after initial crisis (RR=0.53, 95% CI 0.41 to 0.68)
- fewer days in acute care post-crisis (MD= -10.30, 95% CI - 14.77 to -5.83)
- lesser family burden at three months (RR=0.57, 95% CI 0.41 to 0.80) and six months (RR=0.34, 95% CI 0.20 to 0.59)
- higher family satisfaction with treatment at three months (RR=0.63, 95% CI 0.44 to 0.89) and six months (RR=0.57, 95% CI 0.42 to 0.78)
- significantly higher patient satisfaction with treatment at 6 - 20 months

- Crisis resolution and home treatment team provides the following:[22]
  - assessment for admission to acute psychiatric wards
  - initiation of home treatment programme with frequent visits as an alternative to hospitalisation
  - continuation of home treatment until the crisis has resolved and subsequently transfer to other services for further care
  - facilitate early discharge from acute wards

NICE recommends offering crisis resolution and home treatment teams as a first-line service to support people with schizophrenia during an acute episode in the community and should be considered before admission to the hospital and as means to enable timely discharge.[22]

Recommendation 15

- Crisis intervention services should be offered to people with schizophrenia in acute phase.

5.2 Assertive Community Treatment

Assertive community treatment (ACT) is a service that provides continuous care for people with serious mental illness in the community especially those who have difficulty engaging with the mental health services. The Assertive Community Treatment in Schizophrenia Spectrum Disorders (ACCESS II) study showed positive outcomes for those receiving ACT which sustained even after four years:[84, level II-3]

- 75.7% were fully adherent to medications compared with baseline ($p < 0.001$)
- 73.0% received psychotherapeutic treatment conducted by the ACT team or private psychotherapists
- significant reduction of inpatient treatment from 22.4 days at year one to 4.7 days at year four
- significant clinical improvement based on BPRS, CGI-S, GAF and Q-LES-Q

- Key elements of ACT are as follows:[22]
  - a multidisciplinary approach involving a dedicated psychiatrist
  - care for people with serious mental illness
  - shared responsibility for the same client by team members
  - provision of all psychiatric and social care for each client
  - care is provided at home or workplace
  - emphasis on medication adherence

People with schizophrenia should receive ACT if there is a history of poor engagement with services leading to frequent relapse or social disruption, high use of inpatient services and presence of residual psychotic symptoms.[36; 49]

Recommendation 16

- Assertive community treatment should be provided for people with schizophrenia who have difficulties engaging with the mental health services.

5.3 Intensive Case Management

Intensive case management (ICM) is a small case-load (up to 20 people) of community-based psychiatric service for people with serious mental illness that may follow many models e.g. ACT, case management etc. In a large Cochrane systematic review, compared with standard care, people (majority with schizophrenia) receiving ICM had:[85, level I]

- reduced number of days in hospital per month at 24 months (MD= -0.86, 95% CI -1.37 to -0.34)

- reduced number of people living dependently at medium-term (RR=0.80, 95% CI 0.66 to 0.97) and long-term (RR=0.65, 95% CI 0.49 to 0.88)
- improved functioning outcomes based on GAF at long-term (MD=3.41, 95% CI 1.66 to 5.16).
- less likely to be lost to psychiatric services (RR=0.43, 95% CI 0.30 to 0.61)
- significantly higher client satisfaction at short-, medium- and long-term

A recent large cohort study investigated the change in medical utilisation of case management (CM) for psychiatric home care among mainly people with schizophrenia. CM led to a significant decrement of psychiatric and involuntary admissions, and the utilisation shifted toward psychiatric outpatient service. The effect persisted after two years of intervention. However, CM showed no impact on lowering the admission rate for co-morbid physical illnesses.[86, level II-2]

In another cohort study with a long follow-up, ICM significantly improved treatment adherence and reduced suicide and suicidal attempts compared with previous standard treatment received in mental health units. Apart from that, combination of ICM and LAI treatment improved the outcomes.[87, level II-2]

NICE recommends for consideration of ICM for people with psychosis or schizophrenia who are likely to disengage from treatment or services.[22]

Recommendation 17

- Intensive case management should be considered for people with schizophrenia who are at risk of treatment non-adherence.

5.4 Collaborative Community-based Service Intervention

Collaborative community-based service intervention is run by the people in the community who are trained in mental health. This is a strategy to deliver mental health care in low resource setting. The community health workers were defined as non-healthcare workers who had at least 10 years of schooling, good interpersonal skills, systematic training over six weeks and assessment for competency.

An RCT compared collaborative community-based care delivered through community health workers plus standard facility-based care with standard facility-based care alone in schizophrenia. The community-based intervention had better score in the general subscale of PANSS (MD= -2.16, 95% CI -4.23 to -0.09) and locally validated

Indian Disability Evaluation and Assessment (MD= -0.95, 95% CI -1.68 to -0.23) at 12 months.[88, level I]

Recommendation 18
- Collaborative community-based service intervention may be offered for people with schizophrenia.

5.5 Day Hospitalisation/Day Treatment

Day hospital or day treatment centre is an ambulatory treatment programme that emphasises psychosocial and pre-vocational treatment modalities designed for people with serious mental disorders who require co-ordinated, intensive, comprehensive and multi-disciplinary treatment not provided in an outpatient clinic setting.

A Cochrane systematic review found that people with schizophrenia allocated to day hospital care had less admissions to hospital beyond one year compared with those receiving out-patient care (RR=0.71, 95% CI 0.56 to 0.89). The heterogeneity was significant while the quality of primary papers was moderate.[89, level I]

5.6 Residential Services

A quasi-experimental study on people with serious mental illnesses (predominantly schizophrenia spectrum disorders) compared those who were under the Full-Service Partnerships (FSP) programme, which provided a combination of subsidised permanent housing and full-fidelity assertive community treatment, and those receiving public mental health services. FSP participants had significant increase in:[90, level II-1]

- number of days spent in either independent or congregate/ residential living situations
- case management
- medication management
- therapy/rehabilitation
- total outpatient visits

There was also significant decline in:

- mean number of days spent homeless per year
- use of inpatient, emergency and justice system services

On quality of life, FSP clients gave significantly more favorable responses in all domains especially the living situation domain.

In a recent large RCT, there was no significant difference in number of ED visits and hospital admissions between immediate access to independent housing and support from the ACT team also known as

Housing First group and TAU group for people who were homeless with severe mental disorders with predominantly schizophrenia. However, the housing first group showed less inpatient days (RR=0.62, 95% CI 0.48 to 0.80).[91, level I]

- Residential services may be useful in schizophrenia to reduce homelessness.

5.7 Early Intervention in Psychosis

Psychosis can lead to persistent disability, increased cost in treatment, social inequalities and suicide if not intervened early.[22; 92] The initial 3 - 5 years from a first episode of psychosis is a critical period whereby early intervention improves outcomes and alters the trajectory of illness and disability.[22] Early intervention in psychosis consists of early detection of people at risk and phase-specific treatment[93; 94, level I]

Specialised high-risk service is a psychiatric service meant for those at risk of psychosis e.g. in Outreach and Support in South London (OASIS). In a cohort study on patients with first episode psychosis which mainly consisted of schizophrenia at 24 months follow-up, compared with conventional service, OASIS showed significantly:[95, level II-2]

- fewer days in hospital
- shorter median referral-to-diagnosis time
- reduced likelihood of compulsory hospital admission
- lower frequency of admission

In a recent Cochrane systematic review of three RCTs, extended specialised early intervention (SEI) resulted in fewer disengagements from mental health treatment compared with standard SEI + TAU for people with recent-onset psychosis (RR=0.45, 95% CI 0.27 to 0.75). However, there was no significant difference in remission.[96, level I]

People with schizophrenia experiencing first episode of psychosis should receive treatment from the early intervention services which provide a full range of pharmacological, psychological, social, occupational and educational interventions.[22; 36; 49]

- Key elements in early intervention in psychosis services are:[22]
  - swift assessment through a readily accessed point of contact by a practitioner competent in recognising first episode psychosis
  - staff who build up trust and confidence
  - provision of good information on psychosis and treatment options
  - a care coordinator who will support throughout their time in the service, including helping them with self-management skills, social care issues e.g. housing or debt management, and relapse prevention work
  - a choice of psychological and pharmacological interventions
  - support, information and advice for families and carers, including carers' assessments where required
  - support with employment, training and/or education
  - regular physical health checks, monitoring and appropriate treatment, with support and/or education
  - regular monitoring of risk
  - routine monitoring of other co-existing conditions, including depression, anxiety and substance misuse, particularly in the early phases of treatment
  - a crisis plan and prompt service response in crisis

Recommendation 19

- Early intervention in psychosis service should be provided for people with first episode of psychosis.

6. TRADITIONAL AND COMPLEMENTARY MEDICINE

In a Cochrane systematic review, acupuncture added to standard AP may prevent absence of clinical response compared with standard AP in people with schizophrenia at 3 - 12 months follow-up (RR=0.44, 95% CI 0.28 to 0.57). In addition, adverse effects were less in combined treatment (RR=0.30, 95% CI 0.11 to 0.83). However, the certainty of evidence in this review was generally low and of short duration.[97, level I]

In another Cochrane review, yoga as part of a package of care compared with standard care in schizophrenia may have a better QoL at <6 months follow-up (MD=22.93, 95% CI 19.74 to 26.12). This review included a few small studies which lacked many key outcomes.[98, level I]

In a meta-analysis of eight RCTs, extracted Gingko Biloba used as adjunct therapy to AP may improve symptoms of schizophrenia compared with AP alone (SMD= - 0.49, 95% CI -0.69 to -0.30). The certainty of evidence was generally low because most evidence was from short-term trials and graded very low in quality.[99, level I]

- There is insufficient evidence to recommend traditional and complementary medicine in schizophrenia.

7. CHALLENGES IN MANAGEMENT

7.1 Treatment-Resistant Schizophrenia

7.1.1 Definition

The definition for treatment-resistant schizophrenia (TRS) in guidelines on schizophrenia is varied. For clinical purposes, TRS is defined as a condition when patient's symptoms show no response or partial and suboptimal response to trial of two different APs for at least six weeks with each medication used at an adequate dosage of medication. Some definitions specify on using medications from different classes.[36]

Due to lack of uniformity in the definition of TRS, the Treatment Response and Resistance in Psychosis (TRRIP) Working Group has conducted a systematic review and established minimum and optimum criteria to identify TRS for future trials.[100, level I] Refer to **Appendix 9** on **Consensus Criteria for Assessment and Definition of Treatment-Resistant Schizophrenia**. TRS occurs in up to 23% of people with schizophrenia.[101 - 102, level II-2]

7.1.2 Predictors

In the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP-10) study on first episode psychosis in United Kingdom, predicted odds of treatment-resistant schizophrenia (TRS) were 1.09 higher in people with negative symptoms compared with those without negative symptoms. Predicted odds of TRS for people with four and nine negative symptoms were 1.40 and 2.13 respectively.[101, level II-2]

A systematic review of 47 studies showed that clinical predictive factors of TRS were:[103, level I]

- poor premorbid functioning
- male gender
- younger age at onset
- presence of neurobiological factors
- lower educational level
- single marital status
- negative symptoms
- substance use disorder
- non-adherence
- non-response within two weeks of initiation of treatment
- longer duration of untreated psychosis

However, there was no mention of quality assessment in this review.

A Danish cohort study of 4,674 person-years follow-up showed no evidence in polygenic risk score for TRS.[102, level II-2]

7.1.3 Treatment

Four Cochrane systematic reviews studied treatment of TRS. The summary of findings on the effectiveness of pharmacological treatment from the three reviews were:

- clozapine was more effective than typical AP in improvement in BPRS endpoint scores at short-term (WMD= -7.83, 95% CI -10.0 to -5.6) and reduction of relapse rate at long-term (RR=0.17, 95% CI 0.1 to 0.3)[104, level I]
- clozapine showed inconclusive efficacy compared with AAPs which required further trials to confirm the findings[105, level I]
- no significant difference of effect on mental state between very low, low and standard dose of clozapine[106, level I]

For adverse events, the reviews showed:

- comparing with medication typical AP, clozapine caused less movement disorder (RR=0.77, 95% CI 0.7 to 0.9) but more hypersalivation (RR=2.01, 95% CI 1.7 to 2.3) and weight gain (RR=1.33, 95% CI 1.1 to 1.6)[104, level I]
- comparing with AAPs, clozapine produced fewer EPS than risperidone (RR=0.39, 95% CI 0.22 to 0.68) and zotepine (RR=0.05, 95% CI 0.00 to 0.86); however, it caused more reduction in white blood cells count, hypersalivation, sedation, weight gain and seizures than other AAPs[105, level I]
- lower dose of clozapine was associated with less weight gain (MD= -1.60, 95% CI -2.90 to -0.30), lower glucose level after meal (MD= -1.6, 95% CI -2.90 to -0.30) and lower Treatment Emergent Side Effect Scale score (MD= -3.99, 95% CI -5.75 to -2.24)[106, level I]

The quality of primary papers in the reviews varied from moderate to low quality.

Guidelines of SIGN, NICE and APA recommend to offer clozapine to TRS.[22; 36; 49] Refer to **Appendix 7** on **Suggested titration regimen for clozapine initiation in the community** and **Clozapine initiation and titration regimen for in-patient**.

Recommendation 20

- Clozapine should be offered in treatment-resistant schizophrenia.

- **Clozapine augmentation with another medications**

For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare providers should consider the followings before adding a second AP to augment treatment with the clozapine:[22]

  - review the diagnosis
  - ensure adherence to AP (adequate dose and duration)
  - review engagement with psychosocial intervention

- consider other causes of non-response e.g. co-morbid substance misuse disorder (including alcohol, nicotine), concurrent use of other prescribed medication or physical illness

In a Cochrane systematic review, augmentation of clozapine with another APs in five different RCTs (low to very low quality) showed the following results:[107, level I]

- clozapine + aripiprazole vs clozapine + haloperidol
  - no significant differences in mental state based on BPRS at 12, 24 and 52 weeks
  - less side effects in clozapine + aripiprazole based on Liverpool University Neuroleptic Side Effects Rating Scale (LUNSERS) at 12 (MD= -4.90, 95% CI -8.48 to -1.32) and 24 (MD= -4.90, 95% CI -8.25 to -1.55) weeks
- clozapine + amisulpride vs clozapine + quetiapine
  - clozapine + amisulpride showed better CGI score (MD= -0.90, 95% CI -1.38 to 0.42), BPRS score (MD= -4.00, 95% CI -5.86, -2.14), SAPS score (MD= -6.90, 95% CI -12.82 to -0.98) and SANS score (MD= -5.20, 95% CI -7.14 to -3.26) at eight weeks
  - no report on side effects
- clozapine + risperidone vs clozapine + sulpiride
  - clozapine + risperidone had better PANSS positive score at eight weeks (MD= -2.55, 95% CI -4.64 to -0.46)
  - no significant differences in PANSS total score (20% to 50% reduction and mean at end point) and PANSS negative score
  - no significant differences in weight gain and hypersalivation
- clozapine + risperidone vs clozapine + ziprasidone
  - clozapine + risperidone had better HAMD score at six weeks (MD= -3.40, 95% CI -6.71 to -0.09) but not at 26 weeks
  - no significant differences in PANSS, CGI and GAF scores
  - no significant differences in EPS and CGI adverse effect scores
- clozapine + ziprasidone vs clozapine + quetiapine
  - clozapine + ziprasidone had better CGI-S (MD= -0.70, 95% CI -1.18 to -0.22), PANSS total score (MD= -12.30, 95% CI -22.43 to -2.17) and PANSS positive score (MD= -3.10, 95% CI -5.52 to -0.68) at 12 weeks
  - no significant difference in PANSS negative score
  - no significant differences in EPS and overall adverse effect rate

Recommended duration of augmentation to clozapine varies i.e. 8 - 10 weeks[22] or a minimum of 10 weeks.[49]

- Augmentation with AP may be beneficial in people with schizophrenia who did not respond adequately to clozapine.
- Before adding a second AP to clozapine, adequate assessment of the reasons for treatment failure should be conducted.
- The risks and benefits should be weighed if an augmentation treatment is introduced.
- It is important to monitor side effects and potential drug-drug interactions.
- Regular review of the medication regimen should be carried out to justify the continuity of treatment.

- **Electroconvulsive therapy**

A Cochrane systematic review of 15 moderate to low quality RCTs on ECT for TRS showed:[108, level I]

- no significant difference in clinical response compared with clozapine
- improvement in clinical response at short-term (RR=1.91, 95% CI 1.09 to 3.36) and long-term (RR=2.06, 95% CI 1.75 to 2.42) compared with standard care; however, ECT was associated with more memory deterioration (RR=27.00, 95% CI 1.67 to 437.68)
- fewer readmissions (RR=0.29, 95% CI 0.10 to 0.85) compared with sham ECT

In two meta-analyses of moderate to low quality RCTs which compared combination of ECT and AP vs AP alone in patients with TRS, the former had:

- better endpoint improvement in total score of PANSS (SMD= -0.67, 95% CI -0.95 to -0.39)[109, level I] and BPRS (RR=1.25, 95% CI 1.14 to 1.37)[110, level I]
- more side effects
  - headache with NNH of 6 (95% CI 4 to 11)[109, level I] and OR of 9.1 (95% CI 3.97 to 20.86)[110, level I]
  - memory impairment with NNH of 3 (95% CI 2 to 5)[109, level I] and OR of 6.48 (95% CI 3.54 to 11.87)[110, level I]

- ECT in combination with AP may be beneficial in people with treatment-resistant schizophrenia.
- Common adverse reactions e.g. headache and memory impairment should be monitored.

- **Cognitive behaviour therapy**

A large multicentre RCT studied the effectiveness and safety of CBT in clozapine-resistant schizophrenia. The CBT was more effective than TAU in reduction of symptoms severity (PANSS total score) at

nine months (MD= -2.40 points, 95% CI -4.79 to -0.02) but showed no difference at 21 months. There was no significant difference in at least one AE between the two groups.[111, level I]

7.2 Treatment in Special Populations

7.2.1 Co-morbid substance use and tobacco use disorders

People with schizophrenia have been found to have higher rates of substance use disorders (SUD). In a meta-analysis of 123 studies with 165,811 subjects and excluding nicotine dependence, the pooled prevalence of any SUD was 41.7%, with specific prevalence of 27.5% for illicit drugs, 26.2% for cannabis, 24.3% for alcohol and 7.3% for stimulants. The prevalence varies according to geographical distribution and type of substance use.[112, level II-2]

The co-morbidity of SUD among people with schizophrenia carries poorer prognosis and more complex management. Referral to psychiatric services should be considered for these people. SUD should always be considered and monitored across all phases of care for people with schizophrenia.[22]

Evidence on treatment of schizophrenia with co-morbid SUD is limited by scarcity of relevant and high-quality studies. The best option is to offer comprehensive treatment using both pharmacological and psychosocial interventions in treating these patients.

A Cochrane systematic review of eight very low quality RCTs on people with schizophrenia and co-occurring substance misuse showed the following results:[113, level I]

- risperidone vs clozapine
  - clozapine had lower score for endpoint negative symptoms in PANSS (MD=4.00, 95% CI 0.79 to 7.21) but no difference in positive symptoms (MD=0.90, 95% CI -2.21 to 4.01)
  - clozapine had lower scores in craving for substance in Marijuana Craving Questionnaire (MD=7.00, 95% CI 2.37 to 11.63) and Obsessive-Compulsive Craving Scale (MD=14.2, 95% CI 4.45 to 23.95)
  - no significant difference in adherence to AP, EPS and reduction in substance use
- risperidone vs olanzapine
  - no significant difference in reduction of positive symptoms, cannabis use, craving for cannabis and parkinsonism

In a systematic review of 14 studies on patients with schizophrenia and co-morbid substance use disorder, clozapine use in SUD (other than nicotine) was superior than FGA and risperidone in substance use reduction and abstinence. However, it was not superior to olanzapine and ziprasidone. Findings on nicotine use was scarce.[114, level I]

Another meta-analysis involving 19 RCTs on schizophrenia subjects with SUD found that clozapine showed reduction of substance use compared with any APs (MD= -1.08, 95% CI -1.84 to -0.32) while risperidone showed reduction for craving compared with olanzapine (SMD= 0.82, 95% CI 0.18 to 1.46). In terms of symptom reduction, olanzapine, clozapine and risperidone were more effective than other APs. The reported side effects followed the established patterns of each APs. Overall quality of primary studies was of low quality.[115, level I]

Based on a Cochrane systematic review, there was absence of high-quality evidence to support any psychosocial treatment over standard care for important outcomes e.g. remain in treatment, reduction in substance use or improved mental or global state in people with serious mental illnesses and substance misuse. These findings indicated the complexities in the treatment of dual diagnosis.[116, level I]

A meta-analysis of worldwide studies demonstrated an association between schizophrenia and current smoking (OR=5.9, 95% CI 4.9 to 5.7).[117, level II-2] A local study showed the prevalence of nicotine dependence (smoking) among people with schizophrenia in a hospital at 38.1%.[118, level III] This was higher than the overall prevalence of smoking of any tobacco products at 21.3% among Malaysian adults in the National Health and Morbidity Survey 2019.[119, level III]

Guidelines recommend that the attending doctor has to assess the smoking status of all people with schizophrenia.[36; 120] People with schizophrenia should be offered help to stop smoking, even if previous attempts have been unsuccessful.[22]

- **Tobacco cessation**
  - Smoking of tobacco and tobacco products (cigarette, electronic cigarette/vape, shisha, pipe, cigar etc.) can lead to various non-communicable diseases (NCDs). Worldwide, more than eight million people die every year because of this habit.[121]
  - Hence, the decision to integrate smoking treatment with NCDs is important to reduce the prevalence of NCDs and their complications. This decision was made during the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) Steering Committee Meeting in December 2019 chaired by the Honourable Health Minister of Malaysia.
  - The treatment for smoking should be initiated by the treating doctor based on the assessment and treatment of tobacco use disorder as in **Table 4**. Details on this can be found in the CPG on Treatment of Tobacco Use Disorder 2016, available at: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG_TobacoDisorder.pdf

Table 4. Assessment and Treatment of Tobacco Use Disorder

	ASSESSMENT AND TREATMENT
1.	Ask and document smoking status for all patients.
2.	Provide brief advice on quit smoking at every visit to all smokers.
3.	Assess level of nicotine addiction using Modified Fagerström Test for Cigarette Dependence Questionnaire (**COMPULSORY**) and verify smoking status using carbon monoxide breath analyser (**IF AVAILABLE**).
4.	Offer pharmacotherapy to all smokers who are attempting to quit, unless contraindicated.
5.	If selected, use nicotine replacement therapy (NRT) for at least eight to twelve weeks, whereas varenicline should be used for at least twelve weeks.
6.	Combination therapy (e.g. two NRTs, a non-NRT, e.g. bupropion with an NRT) is better than monotherapy in smoking cessation treatment and may be most useful for those smokers at highest risk of relapse.
7.	Use smoking cessation medications with caution in special populations (e.g. children and adolescents, pregnant, breastfeeding women, psychiatric and substance abuse disorder patients).
8.	Arrange a minimum of six to eight face to face follow-up sessions for smoking cessation interventions in six months through counselling support team (health education officer, pharmacists or any officer trained for quit smoking services).

Recommendation 21

- People with schizophrenia and co-morbid substance use disorder should be referred to a psychiatric service for further management.
- People with schizophrenia and smoking should be offered help with smoking cessation.

7.2.2 Pregnancy and breastfeeding

The principles of treatment for pregnant women with schizophrenia should be based on risk-benefit analysis to optimise the outcomes and reduce the complication for both mothers and their babies. The management can be of a great challenge due to the limited availability of evidence. Cohort studies showed that women with schizophrenia had increased risk of complications in pregnancy and delivery, and neonatal morbidity.[122 - 123, level II-2] Postpartum relapse in mothers with schizophrenia in a cohort study was:[124, level II-2]

- highest in 0 to 9 days following childbirth (RR=5.67, 95% CI 3.23 to 9.96), followed by 10 to 19 days after childbirth (RR=4.58, 95% CI 2.48 to 8.48) compared with 180 days after childbirth
- increased if there was admission during pregnancy (RR=6.83, 95% CI 3.58 to 13.04)
- increased when the child's father had a mental disorder (RR=1.80, 95% CI 1.21 to 2.69)

Women with schizophrenia in their reproductive age should receive pre-pregnancy care (PPC) in a nearby health clinic or an obstetric and gynaecology clinic at least three months prior to conception. During PPC, women should be informed regarding their risks and benefits related to conception and during the perinatal period, as well as options for contraception. If she wishes for pregnancy, the treatment of pre-existing schizophrenia must be optimised and the illness is controlled prior to pregnancy. Folic acid supplementation of 5 mg/day should be offered preconceptionally and for the first trimester of pregnancy.[125, level III]

The risks and benefits of continuing AP and consequences of changing treatment must also be discussed, taking into consideration the severity of schizophrenia, risk of relapse, past response to treatment and individual's preference. It is essential to collaborate with the patient, partner and multidisciplinary team in the management of patient throughout the pregnancy and postpartum period.

Pregnant women with schizophrenia should be managed with lowest effective dose using a single AP.[36] Continuing APs in pregnant women with schizophrenia is preferable considering the risk of relapse when they are discontinued, which can further impair the antenatal care, health and social functioning, and mother-infant relationship.[22; 36; 126, level III] Change of treatment is not advisable when a pregnant woman is stable on a specific AP and she is likely to experience relapse of schizophrenia without it.[36] Changing of APs may expose the foetus to two different medications and increases possibilities of relapse in mother.[36; 126, level III]

Limited evidence suggests that FGAs and SGAs have minimal teratogenic risk or toxic effects to the foetus.[126, level III] In a cohort study, women with schizophrenia who received:[127, level II-2]

- FGA and SGA did not show higher odds of babies with low birth weight, small for gestational age or large for gestational age compared with those not receiving APs during pregnancy
- FGA during pregnancy had higher odds of preterm birth (OR=2.46, 95% CI 1.50 to 4.11)

Use of depot preparation during pregnancy should be avoided in order to limit the duration of any possible toxic effect to the foetus.[17]

All APs that have been studied to date cross the placenta, are present in amniotic fluid and excreted in breast milk.[128] Hence, APs withdrawal symptoms can occur in the newborns when they are used in the third trimester. The symptoms are crying, agitation, increased suckling, abnormal increase in tone, tremors, sleepiness, difficulty in feeding and difficulty in breathing which alleviate within hours or days and do not require specific treatment. However, the benefits of treatment for

mothers and newborns superseded the harm of discontinuing APs and generally favours continuation of APs.[129]

Decisions about breastfeeding on exposure to APs in infants and associated benefits and harms should be discussed with all women with schizophrenia.[22] Women taking APs are usually advised to continue the treatment used during pregnancy.[36; 126, level III] Mothers on clozapine should continue the treatment but advised not to breastfeed.[49; 126, level III]

- For lactating mothers, the benefits associated with treatment and risk of exposure to infant are important to be discussed.
- Lactating mother on clozapine are advised not to breastfeed while on treatment.
- For those who do not wish to continue lactating, formula milk supplementation should be offered to the infants.

Refer to **Appendix 5 (Dosing Regimen for Oral Antipsychotics)** and **Appendix 6 (Dosing Regimen for Depot Injections of Antipsychotics)** during pregnancy and breastfeeding.

NICE recommends considering psychological intervention (CBT or family intervention) for women with psychosis or schizophrenia who become pregnant and are at risk of relapse due to:[22]

- stress associated with pregnancy or postnatal period
- change in medication, including stopping APs

Recommendation 22

- Pre-pregnancy care which includes counselling should be offered to all women in reproductive age with schizophrenia.
- Multidisciplinary care should be offered in the management of pregnant women with schizophrenia.

7.2.3 Suicide

- **Prevalence**

The worldwide overall prevalence of suicide in the general population is about 9.0 per 100,000 population (range 2 to 80 per 100,000 population) and it is 2.3 times more common in men compared to women.[130, level III]

A systematic review on the prevalence of suicide in schizophrenia concluded that the life-time risk of suicide among patients with schizophrenia was approximately 5%.[131, level II-2]

A case-control study among 5,650 completed suicides concluded that the overall prevalence of suicide was 11.7% for schizophrenia and related mental disorder with 10.3% in males and 15.7% in females.

In terms of age group, the prevalence was 21.7% in young adults (25 - 34 years old) and 7.7% in elderly (65 years of old). The patients who committed suicide were also most likely coming from the urban poor neighbourhoods, in the younger age group, with more clinically complex presentation and in those with higher rates of mental health service utilisation.[132, level II-2]

- Individuals with schizophrenia account for over 1 in 10 suicide deaths with a life-time risk of about 5%.

- **Risk factors**

A meta-analysis of 96 observational studies concluded that significant risk factors associated with suicide related behaviours in patients with schizophrenia were:[133, level II-2]

- suicidal ideation
  - presence of depressive symptoms
  - higher PANSS general score
  - higher number of psychiatric hospitalisations
- suicide attempts
  - history of alcohol use
  - family history of psychiatric illness
  - physical co-morbidity
  - history of depression
  - family history of suicide
  - history of drug use
  - history of tobacco use
  - presence of depressive symptoms
- completed suicide:
  - male gender
  - history of attempted suicide
  - younger age
  - higher intelligence quotient
  - poor adherence to treatment
  - presence of hopelessness

- The highest risk for suicide in people with schizophrenia is among those who have symptoms of self-devaluation (perceiving oneself to be completely flawed and worthless or as having exaggerated negative qualities and hopelessness).

- **Suicide prevention strategy**

Clozapine is indicated in the treatment of persistent suicidal thoughts or behaviours.[17] APA recommends patients with schizophrenia to be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.[36]

Refer to **Appendix 7** on **Suggested Titration Regimen for Clozapine Initiation in The Community** and **Clozapine Initiation and Titration Regimen for In-Patient**.

Recommendation 23
- Clozapine should be considered in schizophrenia with persistent suicidal risk.

7.3 Social Issues

In a cross-sectional study, the prevalence of perceived stigma was noted to be high at 83.5%. Education status (not able to read and write), difficulties of adherence to AP and duration of illness <1 year were associated factors of the stigma with OR of 2.64 (95% CI 1.12 to 6.23), 4.49 (95% CI 2.31 to 8.73) and 3.48 (95% CI 2.24 to 5.42) respectively.[134, level III]

An RCT showed that psychoeducation programme significantly reduced stigma, improved QoL and medication compliance apart from increased consumer satisfaction of people with schizophrenia and their families, beyond the effects of AP.[135, level I]

Factors that affect and impact social engagement, QoL and life satisfaction for people with schizophrenia were studied in a systematic review of 41 observational studies. A decrease in QoL and social relationships was found due to several factors:[136, level II-2]
- interpersonal relationship status
- employment status
- effects of stigma
- neuro-cognitive skills and functioning
- effectiveness of intervention

However, there was no quality assessment done on the primary papers in the review.

In a cross-sectional study on people with schizophrenia in a hospital, the overall prevalence of psychosocial disabilities was high at 98.1%. The highest prevalence was in social disabilities, followed by vocational, self-hygiene, educational and family-related disabilities.[137, level III]

A population-based study looked into the crime rates in schizophrenia. The overall prevalence of crime in people with schizophrenia was 72.7 to 90.3 per 10,000 from 2012 through 2016, which was about one fifth that of the general population. Further analysis showed that the rates of most types of crimes including violence, intellectual crimes and theft were lower in people with schizophrenia than the general population.

However, the prevalence of murder, arson, and drug-related crimes was about five, six and two times higher in people with schizophrenia respectively.[138, level I]

QualityRights is WHO's global initiative to increase access to good quality mental health services and to promote the human rights of people with psychosocial, intellectual and cognitive disabilities. It offers a new approach to mental health care which is rights-based and recovery-oriented. A pragmatic trial over a 12-month period used QualityRights as an intervention for public mental health services. The core elements of the intervention comprised:[139, level II-1]

- WHO QualityRights toolkit for service assessment
- introduction of service-level policy and processes to protect against inhumane/degrading treatment, violence and abuse (including use of restraints)
- improvements in the service environment within existing service and government resources
- training for healthcare professionals, family members and service users
- peer support volunteers to encourage participation of family members and service users

Compared with usual care, the intervention improved significantly the quality of services in:

- theme 1 (right to adequate standard of living)
- theme 2 (right to enjoyment of highest attainable standards of physical and mental health)
- theme 4 (freedom from torture or cruel, inhumane or degrading treatment or punishment and from exploitation, violence and abuse)

Apart from that, staff in these services showed substantially improved attitudes towards service users (Hedges' g of -0.50 to 0.17)

According to Section 43 of Malaysian Mental Health Regulations 2010, it is made mandatory for every psychiatric hospital to display statements on patient's rights in a conspicuous part of the hospital.[11]

Recommendation 24

- Patient's rights in schizophrenia should be included in the training of healthcare providers and family members.

8. IMPLEMENTING THE GUIDELINES

The management of schizophrenia should be guided by an evidence-based approach, in order to provide quality care to the people with schizophrenia. Several factors may affect the implementation of recommendations in the CPG

8.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

- wide dissemination of the CPG (soft- and hardcopies) to healthcare providers
- training and updates in relation to schizophrenia to healthcare providers
- accessibility to relevant multidisciplinary teams
- public awareness campaigns related to mental health and mental disorders including schizophrenia
- inter-ministerial collaboration and involvement of non-governmental organisations to support the people with schizophrenia and their caregivers

Existing barriers for application of the recommendations of the CPG are:

- limited exposure and training among healthcare providers on management of schizophrenia
- variation in availability of expertise and access to service provision
- insufficient resources in terms of budget, expertise, medications, psychosocial intervention
- socio-cultural barriers and stigma and lack of awareness among patients, families, community and healthcare providers
- lack of local data on schizophrenia, e.g. research, registry, etc., for planning on services

8.2 Potential Resource Implications

This CPG recommends early detection and referral, comprehensive assessment and treatment of schizophrenia. These require increased awareness among healthcare providers, the public and other stakeholders to establish early diagnosis and uninterrupted various forms of treatment as well as support to the patients and their caregivers. Patient-centred care and shared decision making are key elements in successful management in schizophrenia.

However, treatment non-adherence is a widely recognised problem in schizophrenia. This includes failure to start treatment programmes,

default in outpatient clinic appointments and failure to medicate with prescribed APs. The outcome of this discouraging situation is increase in relapse of psychotic symptoms, hospitalisation, aggression, poor QoL, stigmatisation and premature death.

Accordingly, a Key Performance Index for psychiatric service i.e. outpatient defaulter rate is being monitored in both primary and secondary/tertiary care under MoH. By doing so, effective psychosocial interventions e.g. psychoeducation can be targeted to people with schizophrenia. This CPG also recommends that depot APs be prescribed to patients with a history of non-adherence in order to improve their outcomes. Simultaneously, data on depot prescriptions can be captured easily along with the KPI of defaulted patients as a surrogate maker of CPG utilisation based on the recommendation of depot. Moreover, the slightly expensive SGA depots with few intolerance issues and longer injection intervals should be used more widely in the country.

Based on the key recommendations, the following are proposed as clinical audit indicators for quality management of schizophrenia:

Percentage of defaulters* among patients with schizophrenia in outpatient clinic at primary or secondary/ tertiary care (Target of ≤10%) *patients who default one month follow-up

$$= \frac{\text{Number of defaulters among patients with schizophrenia in outpatient clinic at primary or secondary/tertiary care in a period}}{\text{Number of patients with schizophrenia in outpatient clinic at primary or secondary/tertiary care in the same period}} \times 100\%$$

Percentage of patients with schizophrenia having treatment non-adherence prescribed with depot AP (Target of ≥30%)

$$= \frac{\text{Number of patients with schizophrenia having treatment non-adherence prescribed with depot AP in a period}}{\text{Number of patients with schizophrenia having treatment non-adherence in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

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APPENDIX 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: Is intermittent treatment safe and effective compared with continuous treatment for relapse prevention in schizophrenia?

1. SCHIZOPHRENIA/
2. (schizophrenic adj1 disorder*).tw.
3. schizophrenia*.tw.
4. 1 or 2 or 3
5. ANTIPSYCHOTIC AGENTS/
6. (antipsychotic adj1 (agent* or drug* or effect*)).tw.
7. (major tranquili* adj2 agent*).tw.
8. (neuroleptic adj1 (agent* or drug*)).tw.
9. (major adj1 tranquili*).tw.
10. antipsychotic*.tw.
11. neuroleptic*.tw.
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. intermittent.tw.
14. continuous.tw.
15. 13 or 14
16. 12 and 15
17. 4 and 16
18. limit 17 to (english language and humans and yr=”2009 -Current” and “all adult (19 plus years)”)

APPENDIX 2

CLINICAL QUESTIONS

1. What are the risk factors for schizophrenia?
2. What are the accurate screening tools for schizophrenia?
3. What are the cost-effective screening tools for schizophrenia?
4. Is early referral to psychiatric service more effective and safer compared with treatment in primary care?
5. What are the accurate bio-psychosocial assessments in schizophrenia?
6. What are criteria of diagnostic classification of schizophrenia?
7. Is the current diagnostic classification sufficient for therapeutic and prognostic management of schizophrenia?
8. Are the following service level interventions effective and safe in schizophrenia?
   - crisis and emergency service
   - intensive care management
   - assertive outreach team
   - early intervention service
   - community mental health teams
   - day hospitalisation/day care
   - residential care
   - integrating mental health to primary care
   - services in primary care
9. Are the following pharmacological agents safe and effective in schizophrenia?
   - single atypical antipsychotic (AP)
   - single conventional AP
   - combined AP
10. Is rapid escalation of AP/other agents safe and effective in acute exacerbation of schizophrenia?
11. Is depot AP/AAP safe and effective in achieving remission in schizophrenia?
12. Is depot AP/AAP safe and effective in first episode in schizophrenia?
13. Are AAPs more effective and safe compared with conventional APs to prevent relapse in schizophrenia?
14. Is early initiation of AP safe and effective for first episode or early schizophrenia?
15. Is intermittent treatment safe and effective compared with continuous treatment for relapse prevention in schizophrenia?
16. What is the safe and effective treatment for extrapyramidal signs, sedation and weight gain associated with AP?
17. What are the safe and effective physical therapies in schizophrenia?
18. Are the following psychosocial interventions safe and effective (improving function or quality of life) in schizophrenia?

- family therapy
- psychoeducation
- problem solving skill
- counseling and psychotherapy
- Cognitive Behaviour Therapy
- Cognitive Remediation Therapy
- social skills training
- supported employment
- social enterprise
- physical exercise
- peer support services
- life skills training (social and academic)
- creative and expressive art therapy
- religion and spiritual

19. Is traditional and complementary medicine safe and effective in schizophrenia?
20. What is the predictor for treatment-resistant schizophrenia (TRS)?
21. What is the safe and effective AP in TRS?
22. Is augmentation of clozapine with other medication safe and effective in patients who do not respond to clozapine monotherapy?
23. Does pregnancy increase the risk of psychosis development or relapse of schizophrenia?
24. Is AP safe and effective in pregnancy, post-partum and breastfeeding in schizophrenia?
25. Is psychosocial treatment safe and effective in pregnancy, post-partum and breastfeeding in schizophrenia?
26. What is the prevalence of substance-related disorder in schizophrenia?
27. Are the following safe and effective in schizophrenia with substance-related disorder (dual diagnosis):
    - dual diagnosis service vs usual care
    - AP
    - psychosocial treatment
28. What is the prevalence of suicide in schizophrenia?
29. What is the risk factor of suicide in schizophrenia?
30. What is the safe and effective suicide prevention strategy in schizophrenia?
31. What is the prevalence of stigma against schizophrenia?
32. What are the safe and effective strategies to combat stigma in schizophrenia?
33. What is the mental health literacy of schizophrenia among service users?
34. What are the common social problems in schizophrenia?
35. What are the safe and effective interventions for social problems in schizophrenia?

APPENDIX 3

DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA (DSM-5)

The following criteria, as outlined by the DSM-5, must be met in order for schizophrenia to be accurately diagnosed:

A. The individual experiences two or more of the following for a significant portion of time during a 1-month period. And at least one of these must be (1), (2), or (3):
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (incoherence or derailment)
   4. Completely disorganized or catatonic behavior
   5. Negative symptoms, such as diminished emotional expression

B. For a significant amount of time since the disturbance began, level of functioning in one or more major areas (e.g., work, interpersonal relations, or self-care) is clearly below the level achieved prior to onset.
   - In children or adolescents, there is a failure to achieve the expected level of interpersonal, academic, or occupational functioning.

C. Signs of the disturbance continue for 6 months or longer. This period must include at least 1 full month of symptoms that meet the first criteria and may include periods of residual symptoms. During these residual periods, the signs of the disturbance may be manifested only by negative symptoms or by two or more symptoms outlined in the first criteria, only in a lesser form.

D. The disturbance cannot be better explained by schizoaffective disorder, depressive or bipolar disorder because either:
   - No major depressive or manic episodes have occurred concurrently with the active-phase symptoms or if mood episodes have occurred during active phase symptoms, it's been for a minor amount of time.

E. The disturbance cannot be attributed to the physiological effects of a substance (e.g., a drug of abuse or medication) or another medical condition.

F. If the individual has a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is only made if delusions or hallucinations as well as the other required symptoms of schizophrenia are present for a month or more.

G. There are a few specifications that should be made when it comes to diagnosing schizophrenia. This includes specifying the severity, if

it is with catatonia, as well as categorizing it episodically:

- First episode, currently in partial remission: Partial remission refers to a period of time in which the individual has improved after a previous episode is maintained and the criteria are only partially met.
- First episode, currently in full remission: Full remission refers to a period of time after a previous episode during which no symptoms are present.
- Multiple episodes, currently in acute episode: Several episodes may be determined after a minimum of two.
- Multiple episodes currently in partial remission
- Multiple episodes, currently in full remission
- Continuous: Symptoms of the disorder remain for the majority of the illness.
- Unspecified

APPENDIX 4

INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS, 10TH REVISION (ICD 10)

Schizophrenia is coded under F20.

General criteria for Paranoid, Hebephrenic, Catatonic and Undifferentiated type of Schizophrenia:

G1. Either at least one of the syndromes, symptoms and signs listed below under (1), or at least two of the symptoms and signs listed under (2), should be present for most of the time during an episode of psychotic illness lasting for at least one month (or at some time during most of the days).

1. At least one of the following:
   a. Thought echo, thought insertion or withdrawal, or thought broadcasting.
   b. Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, sensations or delusional perception.
   c. Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.
   d. Persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g. being able to control the weather or being in communication with aliens from another world).
2. or at least two of the following:
   e. Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas.
   f. Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech.
   g. Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.
   h. "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).

G2. Most commonly used exclusion criteria: If the patient also meets criteria for manic episode (F30) or depressive episode (F32), the criteria listed under G1.1 and G1.2 above must have been met before the disturbance of mood developed.

G3. The disorder is not attributable to organic brain disease (in the sense of F0), or to alcohol- or drug-related intoxication, dependence or withdrawal.

Pattern of course

F20.x0 Continuous (no remission of psychotic symptoms throughout the period of observation).
F20.x1 Episodic, with a progressive development of 'negative' symptoms in the intervals between psychotic episodes;
F20.x2 Episodic, with persistent but non-progressive 'negative' symptoms in the intervals between psychotic episodes;
F20.x3 Episodic (remittent) with complete or virtually complete remissions between psychotic episodes;
F20.x4 Incomplete remission;
F20.x5 Complete or virtually complete remission;
F20.x8 Other pattern of course.
F20.x9 Course uncertain, period of observation too short.

DOSING REGIMEN FOR ORAL ANTIPSYCHOTICS

Antipsychotics	Daily starting dose (mg/day)	Titration (mg)	Minimum effective dose (mg/day)	Maximum daily dose (mg/day)	Regimen frequency	Chlorpromazine equivalent dose*	Pregnancy safety category[a]	Lactation risk[b]
First-generation APs								
Chlorpromazine	50 - 100	50 - 200/day	200	1000	TDS	100 mg/day (reference)	C	L3
Haloperidol	2 - 5	2 - 5 every 1 - 7 days	2	20	OD/BD	2 mg/day	C	L2
Perphenazine	4 - 8	4 - 8/day	16	24 (64 mg - hospitalised patients)	TDS	10 mg/day	C	NA
Sulpiride	200 - 400	200 every 3 - 7 days	400	2400	BD	200 mg/day	NA	NA
Trifluoperazine	5 - 10	5 every 3 - 7 days	10	30	BD	5 mg/day	C	NA
Second-generation APs								
Amisulpride	50	50 - 100 every 2 - 3 days	300	1200	BD	400 mg/day	NA	NA
Aripiprazole	10 - 15	10 - 15 after 2 weeks	10	30	OD	15 mg/day	C	L3
Asenapine	10	5 - 10 after 1 week	10	30	BD	10 mg/day	C	NA
Brexpiprazole	1	1 for the first 4 days. Then, increased to 2 mg on Day 5 through 7. From Day 8, dose can be increased up to 4	2	4	OD	2 mg/day	NA	NA

Antipsychotics	Daily starting dose (mg/day)	Titration (mg)	Minimum effective dose (mg/day)	Maximum daily dose (mg/day)	Regimen frequency	Chlorpromazine equivalent dose*	Pregnancy safety category[a]	Lactation risk[b]
Cariprazine	1.5	Slow increment of 1.5	1.5	6	OD	1.5 mg/day	NA	NA
Clozapine	12.5	Refer to **Appendix 3** and **4**	300 - 900	900	OD/BD	-	B	L3
Olanzapine	5 - 10	5/day for every 1 week	5	20	OD	10 mg/day	C	L2
Paliperidone	3	3 every 5 days	6 - 12	12	OD	-	C	NA
Quetiapine	IR: 50 ER: 300	IR: Refer to footnote [c] ER: Refer to footnote [d]	IR: 300 - 450 ER: 600 - 800	IR: 750 ER: 800	IR: BD ER: OD	400 mg/day	C	L4
Risperidone	1 - 2	1 every 2 - 3 days	2 - 4	16	OD/BD	4 mg/day	C	L3
Ziprasidone	40 - 80	20 every 2 - 3 days	40	160	BD	80 mg/day	C	L4

IR: immediate release, ER: extended release, OD: once daily, BD: twice daily, TDS: thrice daily, NA: not available
*Chlorpromazine equivalent dose represents the approximate dose equivalent to 100 mg of chlorpromazine (relative potency)
[a]United States Food and Drug Administration (US FDA) categorization of risk of drug use in pregnancy:
A=Controlled studies fail to demonstrate a risk to the foetus in the first trimester, and the possibility of foetal harm remains remote
B=Either animal-reproduction studies have not demonstrated a foetal risk but there is no controlled in human
C=Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in human
D=There is positive evidence of human foetal risk
X=Studies in animals or human beings have demonstrated foetal abnormalities

[b]American College of Obstetricians and Gynecologists lactation risk categories: L1=Safest; L2=Safer; L3=Moderately safe; L4=Possibly hazardous; L5=Contraindicated
[c]Quetiapine IR tablet: Day 1- 25 mg BD, Day 2- 50 mg BD, Day 3- 100 mg BD, Day 4- 150 mg BD. Then adjusted according to response.
[d]Questiapine ER tablet: Day 1- 300 mg OD, Day 2- 600 mg OD. Then adjusted according to response.

Source:

1. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry (14th Edition). London: Wiley Blackwell; 2021
2. British National Formulary (BNF) 80. London: BMJ Group and Pharmaceutical Press; 2021
3. Monthly Index of Medical Specialities – MIMS Malaysia Online (Available at: http://www.mims.com/malaysia)
4. ACOG Practice Bulletin. Clinical Practice Guidelines for Obstetrician-Gynaecologist – Use of Psychiatric Medications During Pregnancy and Lactation

DOSING REGIMEN FOR DEPOT INJECTIONS OF ANTIPSYCHOTICS

Antipsychotics	Starting dose (mg)	Titration (mg)	Dose range (per injection)	Maximum dose	Interval between injections	Chlorpromazine equivalent dose*	Pregnancy safety category[a]	Lactation risk[b]
Aripiprazole	300 mg[c] - 400 mg[d]	Not required	300 - 400 mg every month	400 mg/month	4 weeks	400 mg/month	C	L3
Flupenthixol decanoate	20 mg (elderly - quarter to half adult dose)	Test dose 20 mg, then 20 - 40 mg after at least 7 days, then 20 - 40 mg every 2 - 4 weeks, adjusted according to response	50 mg every 4 weeks to 300 mg every	400 mg/week	2 - 4 weeks	10 mg/week	C	NA
Fluphenazine decanoate	12.5 mg (elderly - 6.25 mg)	Test dose 12.5 mg, then 12.5 - 100 mg after 4 - 7 days, then 12.5 - 100 mg every 14 - 35 days, adjusted according to response	12.5 - 100 mg	100 mg/2 weeks	14 - 35 days	5 mg/week	NA	L3
Paliperidone palmitate	150 mg[e] 175 mg[f]	Refer to footnote [e] and [f]	25 - 150 every 1 month or 175 - 525 mg every 3 months	150 mg/month 525/3 months	1 - 3 months	100 mg/month	NA	NA

Antipsychotics	Starting dose (mg)	Titration (mg)	Dose range (per injection)	Maximum dose	Interval between injections	Chlorpromazine equivalent dose*	Pregnancy safety category[a]	Lactation risk[b]
Risperidone microsphere	25/37.5[g]	Refer to footnote[g]	25 - 50	50 mg/ 2 weeks	2 weeks	50 mg/2 weeks	C	L3
Zuclopenthixol decanoate	100 mg (elderly - quarter to half adult dose)	Test dose 100 mg, then 200 - 500 mg after at least 7 days, then 200 - 500 mg every 1 - 4 weeks, adjusted according to response	200 - 500 mg every 1 to 4 weeks	600 mg/week	1 - 4 weeks	100 mg/week	NA	NA

NA: Not available

*Chlorpromazine equivalent dose represents the approximate dose equivalent to 100 mg of chlorpromazine (relative potency)

[a]United States Food & Drug Administration (US FDA) categorisation of risk of drug use in pregnancy:

A=Controlled studies fail to demonstrate a risk to the foetus in the first trimester, and the possibility of foetal harm remains remote

B=Either animal-reproduction studies have not demonstrated a foetal risk but there is no controlled in human

C=Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in human

D=There is positive evidence of human foetal risk

X=Studies in animals or human beings have demonstrated foetal abnormalities

[b]American College of Obstetricians and Gynecologists lactation risk categories: L1=Safest; L2=Safer; L3=Moderately safe; L4=Possibly hazardous; L5=Contraindicated

[c]CPD2D6 poor metabolisers

[d]Starting dose can be administered following either one regimen (Abilify Maintena®):

1) One injection start: Administer 1 injection 400 mg and continue treatment with 10 mg to 20 mg oral aripiprazole/day for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy

2) Two injection start: Administer two separate injections at separate injection sites, along with one 20 mg dose of oral aripiprazole. After the injection start, the recommended dose range (300 - 400 mg) should be administered once monthly as a single injection (no sooner than 26 days after the previous injection).

[e]Maintenance in patients previously responsive to paliperidone or risperidone (Invega Sustenna®): 150 mg for 1 dose on day 1, then 100 mg for 1 dose on day 8. The third dose subsequently adjusted at monthly intervals according to response.

[f]Maintenance in patients who are clinically stable on once-monthly IM paliperidone (Invega Trinza®): Initially 175 - 525 every 3 months using 3.5-fold higher dose of the last once-monthly dose, adjusted according to response

[g]1) Patient tolerant to risperidone by mouth and taking oral risperidone ≤4 mg daily - Initially 25 mg every 2 weeks, adjusted in steps of 12.5 mg (maximum per dose 50 mg every 2 weeks) at intervals of at least 4 weeks. During initiation, risperidone by mouth may need to be continued for 4 - 6 weeks. Risperidone by mouth may also be used during dose adjustment of depot injection.

2) Patient tolerant to risperidone by mouth and taking oral risperidone >4 mg daily - Initially 37.5 mg every 2 weeks, adjusted in steps of 12.5 mg (maximum per dose 50 mg every 2 weeks) at intervals of at least 4 weeks. During initiation, risperidone by mouth may need to be continued for 4 - 6 weeks. Risperidone by mouth may also be used during dose adjustment of depot injection.

Source:

1. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry (14th Edition). London: Wiley Blackwell; 2021
2. British National Formulary (BNF) 80. London: BMJ Group and Pharmaceutical Press; 2021
3. Monthly Index of Medical Specialities - MIMS Malaysia Online (Available at: http://www.mims.com/malaysia)
4. ACOG Practice Bulletin. Clinical Practice Guidelines for Obstetrician-Gynaecologist - Use of Psychiatric Medications During Pregnancy and Lactation

APPENDIX 7

CLOZAPINE INITIATION AND TITRATION REGIMEN FOR IN-PATIENT

Day	Morning dose (mg)	Evening dose (mg)
1	-	12.5
2	12.5	12.5
3	25	25
4	25	25
5	25	25
6	25	50
7	50	50
8	50	75
9	75	75
10	75	100
11	100	100
12	100	125
13	125	125[a]
14	125	150
15	150	150
18	150	200[b]
21	200	200
28	200	250[c]

Target dose for: [a] female non-smokers (250 mg/day) [b] male non-smokers (350 mg/day) [c] female smokers (450 mg/day)

Treatment breaks and blood monitoring for patients who have been on clozapine for more than 18 weeks:

1. If clozapine is omitted ≥48 hours to ≤72 hours, start at 12.5 mg once or twice a day, gradually increase to avoid the risk of serious AEs (e.g. hypotension, tachycardia, raised temperature). Continue with the established monitoring frequency.
2. If clozapine is omitted >72 hours to <28 days, start at 12.5 mg and titrate up. If no haematologically abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed.
3. If clozapine is omitted ≥28 days, start as new patient, new and pre-treatment result and monitoring same as new commencement for the next 18 weeks of treatment. Start at 12.5 mg and titrate up.

Discontinuation of treatment and blood monitoring:

1. If a patient discontinues treatment, blood monitoring is required at their current monitoring frequency for a period of 4 weeks after stopping.
2. If clozapine is to be stopped for non-haematological reasons or is a planned discontinuation, then a gradual reduction in dose over a 1 to 2-week period is recommended.

Source:

1. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry (14th Edition). London: Wiley Blackwell; 2021
2. Northamptonshire Healthcare NHS. Foundation Trust. Clozapine Treatment Operational Procedures; Oct 2017[140]

SUGGESTED TITRATION REGIMEN FOR CLOZAPINE INITIATION IN THE COMMUNITY

Day	Day of the week	Morning dose (mg)	Evening dose (mg)	Monitoring	Percentage dose of previous antipsychotics
1	Monday	6.25	6.25	A	100
2	Tuesday	6.25	6.25	A	
3	Wednesday	6.25	6.25	A	
4	Thursday	6.25	12.5	A, B, full blood count (FBC)	
5	Friday	12.5	12.5	A Check results from day 4. Remind patient of out-of-hours arrangements for weekend	
6	Saturday	12.5	12.5	No routine monitoring unless clinically indicated	
7	Sunday	12.5	12.5	No routine monitoring unless clinically indicated	
8	Monday	12.5	25	A	75*
9	Tuesday	12.5	25	A	
10	Wednesday	25	25	A	
11	Thursday	25	37.5	A, B, FBC	
12	Friday	25	37.5	A Check results from day 4. Remind patient of out-of-hours arrangements for weekend	
13	Saturday	25	37.5	No routine monitoring unless clinically indicated	
14	Sunday	25	37.5	No routine monitoring unless clinically indicated	
15	Monday	37.5	37.5	A	50*
16	Tuesday	37.5	37.5	Not seen unless problems	
17	Wednesday	37.5	50	A	
18	Thursday	37.5	50	Not seen unless problems	
19	Friday	50	50	A, B, FBC	
20	Saturday	50	50	No routine monitoring unless clinically indicated	
21	Sunday	50	50	No routine monitoring unless clinically indicated	
22	Monday	50	75	A	25*
23	Tuesday	50	75	Not seen unless problems	
24	Wednesday	75	75	A	
25	Thursday	75	75	Not seen unless problems	
26	Friday	75	100	A, B, FBC	
27	Saturday	75	100	No routine monitoring unless clinically indicated	
28	Sunday	75	100	No routine monitoring unless clinically indicated	

Note that much faster titrations can be undertaken in many patients where tolerability allows.
Further increments should be 25 - 50 mg/day (generally 25 mg/day) until target dose is reached.
A. Pulse, postural blood pressure, temperature should be taken before the dose and, ideally, between 30 minutes and 6 hours after the dose. Enquire about AEs.
B. Mental state, weight, review and actively manage AEs (e.g. behavioural advice, slow clozapine titration or reduce dose of other AP, start adjunctive treatments). Consider troponin, C-Reactive Protein, beta-natriuretic peptide.
*May need to be adjusted depending on AEs and mental state.

Source: Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry (14th Edition). London: Wiley Blackwell; 2021

MONITORING PARAMETERS FOR ANTIPSYCHOTICS

Parameter/Test	Suggested frequency	Action if results outside reference range	Drugs with special precautions	Drugs which do not require monitoring
Blood Pressure	Baseline, frequently during dose titration and dose changes to detect AP-induced changes and generally for physical health check	If severe hypotension or hypertension (with clozapine) observed, slower the rate of titration Consider switching to another AP if symptomatic postural hypotension Treat hypertension in line with Malaysia CPG on Management of Hypertension (5th Edition)	Clozapine, chlorpromazine and quetiapine are most likely to be associated with postural hypotension	Amisulpride, aripiprazole, sulpiride
Weight (include waist size and BMI, if possible)	Baseline, frequently for three months then yearly to detect AP-induced changes and generally for physical health check	Offer lifestyle advice Consider changing AP and/or dietary/pharmacological intervention	Clozapine, olanzapine -frequently for three months, then 3-monthly for first year, then yearly	Aripiprazole, ziprasidone are not clearly associated with weight gain but monitoring is required nonetheless – prevalence of obesity is high in this patient group
Full blood count	Baseline and yearly as part of a routine physical health check and to detect chronic bone marrow suppression (small risk associated with some APs)	Stop suspected medication if neutrophils <1.5x109/L Refer to specialist medical care if neutrophils <0.5x109/L Note high frequency of benign ethnic neutropenia in certain ethnic groups	Clozapine - FBC weekly for 18 weeks, then monthly	None

Parameter/Test	Suggested frequency	Action if results outside reference range	Drugs with special precautions	Drugs which do not require monitoring
Plasma glucose - fasting sample if possible	Baseline, at 4 - 6 months, then yearly to detect AP-induced changes and generally for physical health check	Offer lifestyle advice Obtain fasting sample or non-fasting HbA_{1c} Refer to medical specialist/family physician care	Clozapine, olanzapine, chlorpromazine - test at baseline, one month, then 4 - 6 monthly	Some APs are not clearly associated with impaired fasting glycemia, but as its prevalence is high in this patient group, so all patients should be monitored
Urea and electrolytes including creatinine or estimated glomerular filtration rate (eGFR)	Baseline and yearly as part of a routine physical health check	Investigate all abnormalities detected	Amisulpride and sulpiride are renally excreted - consider reducing dose if eGFR reduced	None
Blood lipids (cholesterol, triglycerides) - fasting sample if possible	Baseline, three months, then yearly to detect AP-induced changes and generally for physical health check	Offer lifestyle advice Consider changing AP and/or initiating statin therapy	Clozapine, olanzapine - 3-monthly for first year, then yearly	Some APs (e.g. aripiprazole) not clearly associated with dyslipidaemia, but as prevalence of dyslipidaemia is high in this patient group, so all patients should be monitored
Liver function test (LFT)	Baseline, then yearly as part of a routine physical health check and to detect chronic AP-induced changes (rare)	Stop suspected medication if LFT indicates hepatitis (transaminases x3 normal) or functional damage (prothrombin time/albumin change)	Clozapine and chlorpromazine are associated with hepatic failure	Amisulpride, sulpiride
Prolactin	Baseline, then at six months, then yearly to detect AP-induced changes	Switch drugs if hyperprolactinaemia confirmed and symptomatic Consider tests of bone mineral density for those with chronically raised prolactin	Amisulpride, sulpiride, risperidone and paliperidone are particularly associated with hyperprolactinaemia	Asenapine, aripiprazole, clozapine, quetiapine, olanzapine (<20 mg) and ziprasidone usually do not elevate prolactin, but worth measuring if symptoms arise

Parameter/Test	Suggested frequency	Action if results outside reference range	Drugs with special precautions	Drugs which do not require monitoring
Creatinine phosphokinase	Baseline, then if NMS is suspected	In the psychiatric unit: - stop suspected medication, monitor temperature, pulse, blood pressure - consider benzodiazepines if not already prescribed – IM lorazepam In the medical/emergency unit: rehydration, bromocriptine + dantrolene, sedation with benzodiazepines, artificial ventilation if required	NMS is more likely with FGAs	None
Electrocardiogram	Baseline and when target dose is reached (ECG changes are rare in clinical practice) on admission to hospital and before discharge if medication regimen is changed	Discuss with/refer to medical specialist/family physician care if abnormality detected	Haloperidol, sertindole - ECG is mandatory Ziprasidone - ECG is mandatory in some situations	Risk of sudden cardiac death increased with most APs Ideally all patients should be offered an ECG at least yearly

Adapted:

1. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry (14th Edition). London: Wiley Blackwell; 2021
2. Clinical Practice Guidelines Management of Schizophrenia in Adults. 2009. [Available at: https://www.moh.gov.my/moh/attachments/3882.pdf]

APPENDIX 9

CONSENSUS CRITERIA FOR ASSESSMENT AND DEFINITION OF TREATMENT-RESISTANT SCHIZOPHRENIA

Domain and Subdomain	Minimum Requirement	Optimum Requirement
Current symptoms		
Assessment	Interview using standardised rating scale (e.g., PANSS, BPRS, SANS, SAPS)	Prospective evaluation of treatment using a standardised rating scale
Severity	At least moderate severity	At least moderate severity and <20% symptom reduction during a prospective trial or observation of ≤6 weeks
Duration	≥12 weeks	≥12 weeks; specify duration of treatment resistance
Subjective distress	Not required	Not required
Functioning	At least moderate functional impairment measured using a validated scale (e.g., SOFAS)	Same as for minimum criteria
Adequate treatment		
Assessment of past response	Information to be gathered from patient/carer's report, staff and case notes, pill counts and dispensing charts	Same as for minimum criteria
Duration	≥6 weeks at a therapeutic dosage; record minimum and mean (SD) duration for each treatment episode	Same as for minimum criteria
Dosage	Equivalent to >600 mg of chlorpromazine per day	Same as for minimum criteria
Number of APs	≥2 past adequate treatment episodes with different AP Specify median number of failed antipsychotic trials	≥2 past treatment episodes with different AP and at least one utilising a LAI AP (for at least four months) Specify median number of failed AP trials
Current adherence	≥80% of prescribed doses taken; adherence should be assessed using at least two sources (pill counts, dispensing chart reviews and patient/carer's report) AP plasma levels monitored on at least one occasion Specify methods used to establish adherence	Same as the minimum criteria, with addition of trough AP serum levels measured on at least two occasions separated by at least two weeks (without prior notification to patient)

Domain and Subdomain	Minimum Requirement	Optimum Requirement
Symptom domain	Positive, negative, cognitive	Same as for minimum criteria
Time course	Early onset (within one year of treatment onset), medium-term onset (1 - 5 years after treatment onset), late onset (>5 years after treatment onset)	Same as for minimum criteria
Ultra-treatment resistant: clozapine	Meets the above criteria for treatment resistance plus failure to respond to adequate clozapine treatment	Same as for minimum criteria

Adapted: Howes OD, McCutcheon R, Agid O, et al. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry. 2017;174(3):216-229

LIST OF ABBREVIATIONS

AAP(s)	atypical antipsychotic(s)
ACT	assertive community treatment
AE(s)	adverse event(s)
AGREE II	Appraisal of Guidelines for Research and Evaluation II
AP(s)	antipsychotic(s)
APA	American Psychiatric Association
AUC	area under the curve
BPRS	Brief Psychiatric Rating Scale
B-CATS	Brief Cognitive Assessment Tool for Schizophrenia
CM	case management
CBT	cognitive behaviour therapy
CBT-p	cognitive behaviour therapy for psychosis
CGI-S	Clinical Global Impression Scale
CI	confidence interval
CDSS	Calgary Depression Rating Scale for Schizophrenia
CMHC	community mental health centre
CPG	clinical practice guidelines
CPZ	chlorpromazine
CQ	clinical questions
CrI	credible interval
CT-R	Recovery-Oriented Cognitive Therapy
CRT	cognitive remediation therapy
DG	development group
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
DUP	duration of untreated psychosis
ECG	electrocardiogram
ECT	electroconvulsive therapy
eGFR	estimated glomerular filtration rate
EPS	extrapyramidal side effects
EWS	early warning signs
FGA(s)	first-generation antipsychotic(s)
FSP	full service partnerships
g	gramme
GAF	Global Assessment of Functioning
GRADE	Grading Recommendations, Assessment, Development and Evaluation
GHQ	General Health Questionnaire
HAMD	Hamilton Depression Rating Scale
HTA	Health Technology Assessment
HR(s)	hazard ratio(s)
ICD	International Statistical Classification of Diseases and Related Health Problems
ICM	intensive case management
IM	intramuscular
IQR	interquartile range
IV	intravenous
kg	kilogram
LAI	long-acting injection
LBW	low birth weight
LFT	liver function test
MD	mean difference
mg	milligram

MINI	Mini International Neuropsychiatric Interview
ml	millilitre
MoH	Ministry of Health
ms	millisecond
MSE	mental state examination
ng	nanogram
NICE	National Institute for Health and Care Excellence
NMS	neuroleptic malignant syndrome
NNT(B)	number needed to treat (to benefit)
NNTH	number needed to treat to harm
NSA-4	The 4-item Negative Symptom Assessment
OR	odds ratio
PANSS	Positive and Negative Symptom Scale for Schizophrenia
PPC	pre-pregnancy care
PSP	Personal and Social Performance
PQ-B	Prodromal Questionnaire - Brief Version
QLS	Quality of Life Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QoL	quality of life
RCT(s)	randomised controlled trial(s)
RC	review committee
RR	relative risk
SCID	Structured Clinical Interview for DSM Disorders
SCID-5-CV	Structured Clinical Interview for DSM-5 Disorders-Clinician Version
SCL-90-R	Symptom-Checklist-90-Revised
SEI	specialised early intervention
SGA(s)	second-generation antipsychotic(s)
SMD	standardised mean difference
SPro	Self-screen-Prodrome
SST	social skills training
SUD	substance use disorder
SQ	Screening Questionnaire
TAU	treatment as usual
tDCS	transcranial direct current stimulation
TESS	Treatment Emergent Side Effect Scale
TMS	transcranial magnetic stimulation
TRRIP	Treatment Response and Resistance in Psychosis
TRS	treatment-resistant schizophrenia
US FDA	United States Food and Drug Administration
USD	United States Dollar
vs	versus

ACKNOWLEDGEMENT

The CPG DG members would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft
- Technical Advisory Committee of CPG for their valuable input and feedback
- Health Technology Assessment and Clinical Practice Guidelines Council for approving the CPG
- Dr. Junainah Sabirin, Consultant Public Health Physician on the development of the CPG
- Ms. Rosnani Latip, Ms. Zamilah Mat Jusoh and Ms. Subhiyah Ariffin on retrieval of evidence
- Ms. Sofea Amir on the design cover of the CPG
- All those who have contributed directly or indirectly to the development of the CPG

DISCLOSURE STATEMENT

The panel members of both DG and RC had completed disclosure forms. None held shares in pharmaceutical firms or acts as consultants to such firms. Details are available upon request from the CPG Secretariat.

SOURCE OF FUNDING

The development of the CPG on Management of Schizophrenia (Second Edition) was supported financially in its entirety by the MoH Malaysia while the printing of the CPG was sponsored by the Malaysian Psychiatric Association.

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e ISBN 978-967-2887-32-4