MANAGEMENT OF
MAJOR DEPRESSIVE DISORDER
(Second Edition)

Ministry of Health
Malaysia

Malaysian Psychiatric
Association

Academy of
Medicine Malaysia

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 2019 and will be reviewed in a minimum period of four years (2023) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. 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 is 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 in the process of 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

KEY RECOMMENDATIONS

SCREENING

- Screening for depression using Whooley Questions in primary care may be considered in people at risk.

ASSESSMENT

- The severity of major depressive disorder should be assessed to determine the mode of treatment.

TREATMENT

PSYCHOEDUCATION

- Psychoeducation should be offered early and continuously throughout the management of major depressive disorder.

ACUTE PHASE

- **MILD TO MODERATE**

- In mild to moderate major depressive disorder, psychosocial intervention and psychotherapy should be offered, based on resource availability, but not restricted to the following:
  - cognitive behavioural therapy
  - interpersonal therapy
  - problem-solving therapy
  - behavioural therapy
  - internet-based cognitive behavioural therapy

- **MODERATE TO SEVERE**

- In moderate to severe major depressive disorder, a combination of pharmacotherapy and psychotherapy should be offered.

- In moderate to severe major depressive disorder, exercise may be offered as an adjunct treatment.

- In moderate to severe major depressive disorder, one of the second-generation antidepressants should be prescribed:
  - selective serotonin reuptake inhibitors
  - serotonin noradrenaline reuptake inhibitors
  - noradrenergic and specific serotonergic antidepressants
  - melatonergic agonist and serotonergic antagonist
  - multimodal serotonin modulator
  - noradrenaline/dopamine-reuptake inhibitor

MAINTENANCE AND CONTINUATION PHASE

- Antidepressants should be continued for at least six to nine months after remission, and at least two years if there is a high risk of relapse or recurrence.

MAJOR DEPRESSIVE DISORDER WITH PSYCHOSIS

- Combination of antidepressant and antipsychotic should be considered in major depressive disorder with psychotic features.

FAILED RESPONSE TO INITIAL TREATMENT

- Optimisation of antidepressant should be considered in patients who fail to show response to initial treatment in major depressive disorder.
  - If optimisation fails, refer to a psychiatrist for switching/combination/augmentation options.

TREATMENT-RESISTANT DEPRESSION

- In treatment-resistant depression, the following strategies may be considered:
  - switching antidepressants to a different class
  - combination of antidepressants
  - augmentation with atypical antipsychotics, lithium or antiepileptic agents

PHYSICAL TREATMENT

- Electroconvulsive therapy may be considered in major depressive disorder with:
  - life-threatening conditions e.g. refusal to eat and high suicidality
  - moderate to severe symptoms for rapid improvement in the acute treatment
  - treatment-resistant depression

COLLABORATIVE CARE

- Collaborative care may be considered in acute and continuation phase treatment of major depressive disorder.

MAJOR DEPRESSIVE DISORDER IN PERINATAL WOMEN

- Screening for perinatal depression may be done in a two-stage approach.
  - Use brief screening tools e.g. Patient Health Questionnaire-2 or Whooley Questions in the first stage.
  - If there is positive response to the brief screening tools, Edinburgh Postnatal Depression Scale should be used for further screening

- For mild to moderate perinatal depression, psychotherapy, e.g. interpersonal psychotherapy and cognitive behavioural therapy, should be considered as initial treatment.
- Psychosocial interventions, i.e. peer support and non-directive counselling, may be considered in mild to moderate postpartum depression.
- For severe perinatal depression, pharmacotherapy should be considered and selective serotonin reuptake inhibitors are the preferred choice. Once medications have become effective, psychotherapy may be offered as an adjunct.

MAJOR DEPRESSIVE DISORDER IN THE ELDERLY

- Antidepressants should be considered with caution on tolerability issues for major depressive disorder in the elderly.
- Psychotherapy should be offered for major depressive disorder in the elderly.
- Electroconvulsive therapy may be offered in elderly with major depressive disorder after assessment of possible co-morbidities.

MAJOR DEPRESSIVE DISORDER IN PATIENTS WITH CHRONIC MEDICAL ILLNESS

- Screening for depression should be done in patients with chronic medical illness (CMI) with related functional impairment.
- Psychosocial intervention and psychotherapy should be considered in patients with major depressive disorder and CMI.
- If pharmacotherapy is required for patients with major depressive disorder and CMI, consider antidepressants with the least drug-drug interactions.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the development group (DG) for this CPG were from the Ministry of Health (MoH) and Ministry of Education. There was an 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 inclusion criteria are all adult patients with major depressive disorder (MDD) regardless of study design. The search was limited to literature published from 2006 and on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched further to look for relevant studies. Experts in the field were also contacted to identify relevant studies. All searches were conducted from 6 March 2016 to 15 August 2018. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 22 February 2019 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 made to other CPGs on MDD e.g.
- Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for Mood Disorders (Royal Australian and New Zealand College of Psychiatrists, 2015)
- Mental Health Care in the Perinatal Period [Centre of Perinatal Excellence (COPE) 2017]
- Clinical Guidelines for the Management of Adults with Major Depressive Disorder [Canadian Network for Mood and Anxiety Treatments (CANMAT), 2016]
- Depression, The Treatment and Management of Depression in Adults (Updated Edition) (National Collaborating Centre for Mental Health, 2010)
- MOH Clinical Practice Guidelines: Depression (MoH Singapore, 2012)
- Depression in Adults with a Chronic Physical Health Problem (National Collaborating Centre for Mental Health, 2010)

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

A total of 11 main clinical questions were developed under three different sections (screening, treatment and monitoring). Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 21 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using the Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in DG meetings. All statements and recommendations subsequently 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 is based largely 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 strictly follows the requirement of AGREE II.

On completion, the draft 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 Health Technology Assessment (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/penerbitan/mymahtas/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the management of MDD in the following aspects:
  a) diagnosis
  b) treatment
  c) monitoring

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

a. Inclusion Criteria
Adult patients with MDD

b. Exclusion Criteria
  • Persistent depressive disorder
  • Depressive episodes in patients with bipolar disorder or adjustment disorder with depressed mood

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care in the management of MDD including:
  i.   doctors
  ii. allied health professionals
  iii. trainees and medical students
  iv. policymakers
  v.   patients and their advocates
  vi. professional societies

HEALTHCARE SETTINGS

Primary and secondary/tertiary care settings

DEVELOPMENT GROUP

Chairperson

Dr. Uma Visvalingam
Consultant Psychiatrist
Hospital Putrajaya, Putrajaya

Members (in alphabetical order)

Ms. Aida Farhana Suhaimi
Clinical Psychologist
Hospital Putrajaya, Putrajaya

Dr. Aida Syarinaz Ahmad Adlan
Senior Lecturer & Psychiatrist
University Malaya Medical Centre
Kuala Lumpur

Dr. Firdaus Abdul Gani
Consultant Psychiatrist
Hospital Sultan Haji Ahmad Shah
Temerloh, Pahang

Dr. Masseni Abd Aziz
Family Medicine Specialist
Klinik Kesihatan Umbai, Melaka

Dr. Mohd Aminuddin Mohd Yusof
Head of CPG Unit & Public Health
Physician
MaHTAS, Ministry of Health, Putrajaya

Associate Professor Dr. Muhammad
Muhsin Ahmad Zahari
Senior Consultant Psychiatrist
University Malaya Medical Centre
Kuala Lumpur

Dr. Noor Izuana Redzuan
Consultant Psychiatrist
Hospital Putrajaya, Putrajaya

Dr. Noormazita Misran
Consultant Psychiatrist
Hospital Tuanku Jaafar
Seremban, Negeri Sembilan

Ms. Nurul Syakilah Embok Raub
Principal Assistant Director
Pharmacy Practice & Development
Division Ministry of Health, Selangor

Dr. Peter Low Kuan Hoe
Consultant Psychiatrist
Hospital Bahagia Ulu Kinta, Perak

Ms. Siti Mariam Mohtar
Senior Assistant Director
MaHTAS, Ministry of Health, Putrajaya

Associate Professor Dr. Suzaily Wahab
Lecturer & Consultant Psychiatrist
Hospital Canselor Tuanku Muhriz
Universiti Kebangsaan Malaysia
Medical Centre, Kuala Lumpur

Dr. Tan Sing Yee
Family Medicine Specialist
Klinik Kesihatan Jenjarom, Selangor

Dr. Umi Adzlin Silim
Consultant for Consultation-Liaison
Psychiatry
Hospital Kuala Lumpur, Kuala Lumpur

REVIEW COMMITTEE

The draft guidelines were reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

Chairperson

Dr Toh Chin Lee
National Advisor for Psychiatry
Head of Department & Consultant Psychiatrist
Hospital Selayang, Selangor

Members (in alphabetical order)

Dr. Azizul Awaluddin
Head of Department & Consultant Psychiatrist
Hospital Putrajaya, Putrajaya

Dr. Baizury Bashah
Consultant Family Medicine Specialist
Klinik Kesihatan Kuala Lumpur, Kuala Lumpur

Dr. Junainah Sabirin
Deputy Director & Public Health Physician
MaHTAS, Ministry of Health, Putrajaya

Dr. Lim Chong Hum
Consultant Psychiatrist & Clinical Epidemiologist
Ramsay Sime Darby/ParkCity Medical Centre, Selangor

Dr. Norhayati Nordin
Hospital Director & Consultant Psychiatrist (Child & Adolescents)
Hospital Bahagia Ulu Kinta, Perak

Associate Professor Dr. Normala Ibrahim
Deputy Dean (Research and Internationalization) & Consultant Psychiatrist
Universiti Putra Malaysia, Selangor

Ms. Noor Ratna Naharuddin
Pharmacist
Hospital Sultan Ismail, Johor

Professor Dr. Nor Zuraida Zainal
Consultant for Consultation-Liaison Psychiatry
University Malaya Medical Centre, Kuala Lumpur

Ms. Raynuha Mahadevan
Lecturer & Clinical Psychologist
Hospital Canselor Tuanku Muhriz
Universiti Kebangsaan Malaysia, Kuala Lumpur

EXTERNAL REVIEWERS (in alphabetical order)

Dr. Ang Jin Kiat
Senior Lecturer & Psychiatrist
Universiti Putra Malaysia, Selangor

Professor Dr. Anne Buist
Professor of Women's Mental Health
University of Melbourne, Austin Health
Australia

Dr. Cheah Yee Chuang
Consultant Community &
Rehabilitation Psychiatrist
Hospital Bahagia Ulu Kinta, Perak

Professor Dr. David J. Kupfer
Professor Emeritus of Psychiatry
University of Pittsburgh
United States of America

Professor Dr. Firdaus Mukhtar
Head of Department & Clinical
Psychologist
Universiti Putra Malaysia, Selangor

Professor Dr. Hatta Sidi
Senior Lecturer & Senior Consultant
Psychiatrist
Pusat Perubatan Universiti Kebangsaan
Malaysia, Kuala Lumpur

Dr. Idayu Maarof
Registered Medical Practitioner
(General Practitioner) &
Patient Advocate
Shah Alam, Selangor

Professor Dr. Mohamad Hussain Habil
Senior Lecturer & Senior Consultant
Psychiatrist
MAHSA University, Selangor

Dr. Muniswaran a/l Ganesham @
Ganeshan
Maternal-Fetal Medicine Specialist &
Ostetrician and Gynaecologist
Hospital Wanita & Kanak-kanak
Kuala Lumpur, Kuala Lumpur

Dr. Rozita Mat Zin
General Practitioner & Patient Advocate
Klinik Wong Singh
Bandar Country Homes, Selangor

Dr. Salmah Noordin
Consultant Family Medicine Specialist
Klinik Kesihatan Batu 9, Cheras,
Selangor

Dr. Sarfraz Manzoor Hussain
Consultant Psychiatrist
Nilai Medical Centre, Negeri Sembilan

Mr. Syahrir Zaini
Lecturer & Pharmacist
International Islamic University Malaysia
Pahang

Dr. Zanariah Mat Saher
Consultant Geriatric Psychiatrist
Hospital Kuala Lumpur, Kuala Lumpur

ALGORITHM 1. TREATMENT OF MAJOR DEPRESSIVE DISORDER

DIAGNOSIS

Phases of treatment

ACUTE
- To achieve remission

CONTINUATION AND MAINTENANCE
- To prevent relapse, recurrence and development of chronicity

TREATMENT

Mild to moderate

Psychosocial intervention + Psychotherapy ± Pharmacotherapy

Moderate to severe

Pharmacotherapy + Psychotherapy + Psychosocial intervention ± ECT

Psychotic features

Pharmacotherapy + Psychosocial intervention ± ECT

CONTINUATION AND MAINTENANCE

Pharmacotherapy + Psychosocial intervention **AND/OR** Psychotherapy + Psychosocial intervention

ECT = electroconvulsive therapy

ALGORITHM 2. PHARMACOTHERAPY FOR MAJOR DEPRESSIVE DISORDER

Diagnosis of MDD

Consider factors for choice of antidepressant [refer to **Chapter 4.1.2 (B)**]

Start second-generation antidepressant*

Response** after 2 - 4 weeks

No → ***Consider factors for initial treatment failure and manage accordingly

Yes

Optimise by titrating dose of medication as tolerated

Adequate response after 2 weeks of optimisation

Yes → **Remission**

No****

Continuation/ maintenance phase treatment
- 6 - 9 months after onset of remission
- ≥2 years if there is a high risk of relapse and recurrence

Other strategies:
- switching antidepressants to a different class
- combination of antidepressants
- augmentation with AAP/lithium/AED

*Second-generation antidepressants: SSRIs, SNRIs, NaSSAs, melatonergic agonist and serotonergic antagonist, multimodal antidepressants and NDRIs
Refer to **Chapter 3
***Consider:
- Incorrect diagnosis (e.g. failure to diagnose bipolar disorder)
- Psychotic depression
- Organic conditions e.g. anaemia or hypothyroidism
- Co-morbid psychiatric disorder e.g. substance abuse or dependence, panic disorder, obsessive-compulsive disorder and personality disorder
- Adverse psychosocial factors
- Non/poor compliance
****Consider referral to psychiatrist

MDD	= major depressive disorder
AAP	= atypical antipsychotics
AED	= antiepilectic drugs
SSRIs	= selective serotonin reuptake inhibitors
SNRIs	= serotonin noradrenaline reuptake inhibitors
NaSSAs	= noradrenergic and specific serotonergic antidepressants
NDRI	= noradrenaline/dopamine-reuptake inhibitors

ALGORITHM 3. TREATMENT OF PRE-EXISTING MAJOR DEPRESSIVE DISORDER IN PRE-PREGNANCY, PREGNANCY & POSTPARTUM PERIOD

Pre-existing Major Depressive Disorder (MDD) in Pre-Pregnancy, Pregnancy and Postpartum Period

Mild MDD not on antidepressant

Moderate - Severe MDD

Expedite psychosocial intervention and psychotherapy with close monitoring of symptoms

On antidepressant

Not on antidepressant

Assess risk and benefit of continuing antidepressant treatment and consequences of stopping abruptly or changing treatment

Assess risk and benefit of starting antidepressant treatment and consequences of no treatment

Continue antidepressant

Switch antidepressant

Stop antidepressant

Start antidepressant

No antidepressant

Consider combination with psychotherapy

Consider antidepressant with lower risk to pregnancy and breastfeeding with close monitoring of symptoms

Expedite psychotherapy with close monitoring of symptoms

Consider combination with psychotherapy with monitoring of symptoms

Expedite psychotherapy with close monitoring of symptoms

ALGORITHM 4. TREATMENT OF NEWLY DIAGNOSED MAJOR DEPRESSIVE DISORDER IN PREGNANCY AND POSTPARTUM

Newly Diagnosed Major Depressive Disorder (MDD), Peripartum Onset

Mild - Moderate MDD

Start psychosocial intervention and psychotherapy

Moderate - Severe MDD

Assess risk and benefit of antidepressant treatment and consequences of no treatment

Start antidepressant

Consider combination with psychosocial intervention and psychotherapy

No antidepressant

Expedite psychosocial intervention and psychotherapy with close monitoring

1. INTRODUCTION

Mental health is a state of well-being in which every individual realises his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to the community.[1] It includes emotional, psychological and social well-being. However, unhealthy mental health can lead someone to develop mental disorder including MDD. Mental disorder is defined as "a syndrome characterised by clinically significant disturbance in an individual's cognition, emotion regulation or behaviour that reflects a dysfunction in the psychological, biological or developmental processes underlying mental functioning".[2]

MDD, a common but complex illness, can present with a variety of unique symptom combinations. This disorder is characterised by persistent low mood, loss of interest, difficulty in concentrating, sleep disturbances, fatigue and in more severe form, functional impairment and suicidal ideations. Functional impairment is defined as loss of functional capacity affecting a person's ability to work resulting from the person's medical condition.[3]

It is estimated that MDD will contribute to highest burden of disease in 2030.[4] The adverse outcomes related to MDD varies from significant difficulties in role transitions, decreased role functioning, increased risk of onset, severity and persistence of several secondary disorders. There is higher risk of early mortality resulting from physical disorders and suicide.[5, level III] The World Health Organization (WHO) reported that suicide is the second leading cause of death among the 15 to 29 years age group.[6]

A review of depression studies in Malaysia showed the prevalence of MDD in Malaysia to be between 8 - 12%.[7, level III] A meta-analysis showed a global prevalence of MDD at 4.7% (95% CI 4.4 to 5.0%).[8, level III]

A systematic review of 27 studies showed that MDD (especially in specialised mental health care) often has a chronic and/or recurrent course with consequences over the entire lifespan.[9, level III] WHO Global Health Estimates 2015 found that depressive disorders contribute to 7.5% of total Years Living with Disability (YLD) worldwide and this translates as the single largest contributor to global disability. According to this report, MDD contributes to 6.9% of total YLD in Malaysia.[10]

To ensure full functional recovery and prevention of relapse, the targeted outcome for treatment of MDD is treatment to remission. Remission can be defined as a minimum of 80% reduction in symptoms of MDD or as an absolute cut-off score in any one validated rating scales.[11, level III] Non-remission of depressive symptoms in MDD has implications on functionality[12, level II-2] and can add to the economic burden of the illness.

This CPG is a full review of the previous edition of guidelines on the Management of MDD published in 2007. In order to preserve the validity of these guidelines, new evidence in the management of MDD was searched and critically appraised prior to being accepted. This CPG also minimises variation in clinical practices to adapt appropriate management in MDD.

2. ASSESSMENT AND DIAGNOSIS

2.1 Screening

In a systematic review of local studies in Malaysia, prevalence of depression in primary care ranged from 6.7% to 14.4%. Among the elderly in the general community, the prevalence was between 6.3% and 18%. In most of the studies, women had higher rates of depression than men. Studies in a clinical setting found a prevalence of depression to be 20.7% in post-partum women, 36% in post-stroke patients and 19.1% in breast cancer patients. However, different instrument were used in these studies.[13, level III]

The US Preventive Services Task Force (USPSTF) guidelines recommend screening for depression in adults, including perinatal women. It should be implemented when there are adequate systems in place to ensure accurate diagnosis, effective treatment and appropriate follow-up.[14] However, in the absence of benefit in screening and presence of potential harms, the Canadian Preventive Task Force guidelines do not recommend routine screening for depression in primary care settings, either in adults at average risk or in those with characteristics that may increase their risk of depression.[15]

The CPG DG suggests screening for depression in high risk individuals with following history:[16, level III]
- first-degree relative with a history of depression
- chronic diseases
- obesity
- chronic pain (e.g. backache, headache)
- impoverished home environment
- financial constraint
- experiencing major life changes
- pregnant or postpartum period
- socially-isolated
- multiple vague symptoms
- sleep disturbance
- substance abuse (e.g. alcohol, illicit drugs)
- loss of interest in sexual activity
- old age

> - There is insufficient evidence to perform screening for depression in the general population.

The common tools used in Malaysia for screening of depression are Beck Depression Inventory (BDI), Depression, Anxiety and Stress Scale (DASS), Patient Health Questionnaire-9 (PHQ-9), and Hospital

Anxiety Depression Scale (HADS). All these screening tools have validated Malay version.[17, level III] Besides that, Whooley Questions is a shorter tool which has been validated locally.[18, level III]

> • Whooley Questions on depression:
>   ○ "During the past month, have you often been bothered by feeling down, depressed or hopeless?"
>   ○ "During the past month, have you often been bothered by having little interest or pleasure in doing things?"

The screening of depression with the Whooley Questions in the primary care shows a sensitivity of 96% to 99% and a specificity of 70% to 78%. The addition of the help question (Do you need help?) increases the specificity to 95%.[18 - 19, level III] The Whooley Questions may be considered in people who may have depression particularly in those with a past history of depression or a chronic physical health problem with associated functional impairment.[20]

> **Recommendation 1**
> • Screening for depression using Whooley Questions in primary care may be considered in people at risk*.

*Refer to preceding text.

Refer to **Appendix 6A** for **Malay version of Whooley Questions**.

2.2 Assessment

Assessment of depression consists of detailed history taking, mental state examination, physical examination and investigations where indicated:[21]

History taking include:
- presenting symptoms
- mode of onset
- duration and severity of symptoms
- number and severity of past episodes
- response to treatment
- previous hospitalisations
- psychosocial stressors
- family history
- suicide attempts
- past history of manic or hypomanic episodes
- substance abuse or other psychiatric illnesses
- social history and social support

- social and occupational impairment
- relevant medical history
- drugs history (prescribed and over-the-counter medications)

Mental state examination include:
- evaluation of depressive symptom severity
- presence of psychotic symptoms
- risk of harm to self and others

Physical examination should be done accordingly to rule out any medical or surgical causes for depressive symptoms. Laboratory tests may be required, particularly if the presentation is atypical e.g. symptoms suggesting a medical cause, elderly patients, first major depressive episode after the age of 40, absence of precipitating factors and depression not responding fully to the standard treatment.[21]

2.3 Diagnosis and Assessment of Severity

The diagnosis of MDD is made using internationally accepted diagnostic criteria i.e. either the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) or the ICD-10 Classification of Mental and Behavioural Disorder: Clinical Description & Diagnostic Guidelines.

Based on the DSM-5 criteria, a minimum of five symptoms is required to diagnose MDD (refer to **Appendix 3**).

Assessment of MDD severity is important to determine the mode of treatment. The assessment is determined by the total number of symptoms criteria, the severity of symptoms and the extent of functional disability.

According to DSM-5, the severity of MDD can be divided into mild, moderate and severe. For mild depression, five or more symptoms are present which cause distress but they are manageable and result in minor impairment in social or occupational functioning. For severe depression, most of the symptoms are present with marked impairment in functioning. It can present with or without psychotic symptoms. For moderate depression, both symptom presentation and functional impairment lies between the above two severities.

Another classification of the depression severity is based on ICD-10 criteria (refer to **Appendix 4**).

The DSM-5 is widely used in clinical practice and research in local setting.

> **Recommendation 2**
> • The severity of major depressive disorder should be assessed to determine the mode of treatment.

2.4 Suicide Risk Assessment

A recent systematic review found that the suicide rate in Malaysia is approximately 6 - 8/100,000 population/year with a rising trend in the means of suicide and self-harm.[22, level III] The risk of suicide among hospitalised patients with severe MDD can be as high as 15%.[21] Thus, thorough suicide risk assessment should be emphasised in a comprehensive management of MDD. Locally, the Malaysian Guidelines on Suicide Prevention & Management and Guidelines on Suicide Risk Management in Hospitals were developed to assist practitioners in suicide preventive measures.

A systematic review of 21 studies evaluating 15 suicide risk assessment instruments on a group of suicide attempters, showed that none fulfilled requirements for diagnostic accuracy and there was insufficient evidence to support its use in predicting suicidal acts.[23, level II-2] A recent multicentre, population-level cohort study on individuals with self-harm episodes, suggested that suicide risk assessment scales should not be used alone to determine treatment options or predict future risk of further self-harm or suicide.[24, level II-2] Therefore, suicide risk assessment instruments should only be used to complement a detailed clinical assessment and a structured follow-up management plan, while building a good therapeutic alliance with the patients.

Assessment of suicide intent is a vital measurement to evaluate future suicide risk among patients who self-harm.[25, level II-2] Hence, measurement of this risk should be included during the risk assessment and can be done using specific tools (e.g. Beck Suicide Intent Scale).

The suicide risk factors are:[21]
- loss of relationship
- financial or occupational difficulties
- poor social support
- past suicide attempt
- family history of suicide
- alcohol abuse/dependence
- other medical co-mordibities
- suicidal ideations
- severity of depression
- psychomotor agitation
- low self-esteem
- hopelessness

2.5 Referral and Admission
2.5.1 Criteria for referral to psychiatric services
There is no new retrievable primary paper on referral of MDD. The previous MoH CPG is used for this section.[21] Communication between healthcare personnel and patients has to be clear in explaining the needs and benefits of psychiatric interventions.

- In a local setting, referral to the psychiatric services may be done through the emergency and trauma department or directly to the psychiatric clinic. Indications for referral to psychiatric services include:[21]
  - unsure of diagnosis
  - attempted suicide
  - active suicidal ideas
  - failure of treatment
  - advice on further treatment
  - clinical deterioration
  - recurrent episode within one year
  - psychotic symptoms
  - severe agitation
  - self-neglect

2.5.2 Criteria for admission
Admission of patients with MDD may be required if outpatient care alone is insufficient. Locally, admission to the psychiatric ward can be voluntary or involuntary according to the Mental Health Act (2001).[26] Indications for admission are as follows:[21]
- risk of harm to self
- psychotic symptoms
- inability to care for self
- lack of impulse control
- danger to others

3. PHASES OF TREATMENT

General principles of MDD treatment are:
- to relieve symptoms
- to reduce the morbidity and disability
- to limit risks of self-harm and fatality

Treatment of MDD can be divided into three phases - acute, continuation and maintenance (refer to **Figure 1**). For the purpose of discussion in this CPG, the continuation phase is considered as part of the maintenance phase.
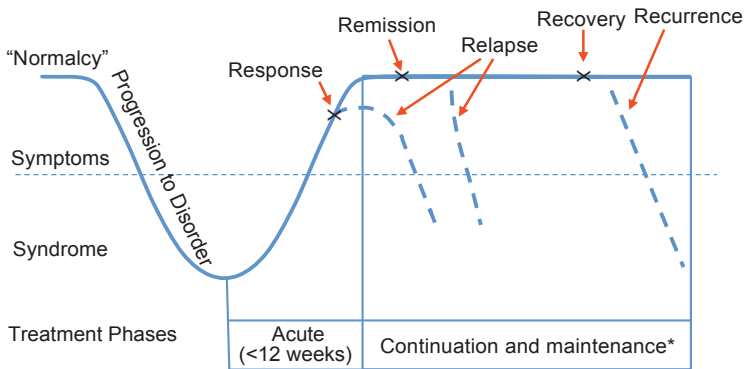
Figure 1. Phases of treatment of major depression

Adapted: Kupfer DJ. Long-term treatment of depression. J Clin Psychiatry 1991:52 (Suppl):28-34

*Refer to **Subchapter 4.2.1 B** on **Pharmacotherapy**.

- The acute phase is a period aiming to achieve remission.[21]
- The maintenance phase is a period to prevent relapse and recurrence and, development of chronicity.[27]
- Response is a ≥50% reduction in depressive symptoms and at least a moderate degree of global improvement.[21]
  - Non-response - ≤25% decrease in baseline symptom severity
  - Partial response - >25% and <50% decrease in baseline symptom severity
- Remission is the absence of signs and symptoms in the current episode of depression and restoration of function.[21]
- Relapse is the return of symptoms of the current episode within six months following remission.[28]
- Recovery is when an individual is fully functional and has returned to premorbid functioning.[29]
- Recurrence is a new episode of depression after recovery.

4. TREATMENT

The modalities of treatment in MDD are:
- pharmacotherapy
- psychotherapy
- psychosocial intervention
- physical
- others

These are offered based on the severity of the disease (mild, moderate and severe) in both acute and maintenance phases. Refer to **Appendix 8** on **Suggested Antidepressant Dosages and Adverse Effects**.

4.1 Acute Phase
4.1.1 Mild to Moderate
A. Psychosocial Interventions and Psychotherapy

Evidence on the effectiveness of psychological and psychosocial interventions have mainly been found in the acute treatment of MDD, and mostly between mild to moderate severity. The general aim of these interventions is to alleviate core depressive symptoms or prevent symptoms recurring.

There are psychological and psychosocial interventions of lower intensity that are less dependent on trained professionals and can be self-guided (e.g. internet- and mobile-based intervention, exercise programme, etc.).[20, 29]

The types of interventions offered depends on patient's preferences and attitudes, therapist competence, therapeutic alliance and availability of the intervention.[20, 30]

Psychosocial Interventions
i. Psychoeducation

Psychoeducation is given by delivering information on pharmacotherapy and psychological measures which consist of topics on:
- symptoms and course of depression
- the biopsychosocial model of aetiology
- pharmacotherapy for acute phase and maintenance
- drug side effects and complications
- importance of medication adherence
- early signs of recurrence
- management of relapse and recurrence

Psychoeducation is an important component in the treatment of depression. It is provided early and continuously throughout the management of the condition.

In patients with <5 episodes, there was no difference between manualised psychoeducation as an adjunct to an antidepressant in preventing relapse than maintenance cognitive behavioural therapy (CBT). However, in those with ≥5 previous major depressive episodes, manualised psychoeducation is significantly less effective in similar comparison.[31, level I]

A randomised controlled trial (RCT) showed that adding a family intervention to inpatient treatment of MDD over TAU improved BDI scores (p<0.005). It was also more effective in improving subjective emotional health in patients' partners at three months follow-up (p=0.029).[32, level I]

> **Recommendation 3**
> • Psychoeducation should be offered early and continuously throughout the management of major depressive disorder.

ii. Counselling/Non-directive Supportive Therapy
The British Association for Counseling and Psychotherapy defines counselling as 'a systematic process which gives individuals an opportunity to explore, discover and clarify ways of living more resourcefully, with a greater sense of well-being'.[20] It is commonly described in the literature as either non-directive supportive therapy (NDST) or supportive therapy.

An RCT of primary care patients found that there was no significant difference between counselling and CBT in reducing BDI score at four months in MDD.[33, level I] A meta-analysis of 31 RCTs of moderate quality primary papers found that NDST was more effective than waiting list or usual care (Hedges' g=0.58, 95% CI 0.45 to 0.72; NNT=3) but less effective than other psychotherapies (Hedges' g= -0.20, 95% CI -0.32 to -0.08) in mild to moderate MDD.[34, level I]

iii. Peer Intervention
Peer intervention, which includes peer support and self-help groups, is often used as a complement to clinical care. CANMAT recommends peer intervention as a second-line adjunctive treatment for MDD.[30]

A meta-analysis of seven RCTs found that peer support interventions were more effective compared with usual care in reducing depressive symptoms in adults with depression (SMD= -0.59, 95% CI -0.98 to -0.21). However there was no significant difference between peer intervention and group CBT in MDD for the same outcome.[35, level I]

iv. Exercise
Exercise is defined as the 'planned, structured and repetitive bodily movement done to improve or maintain one or more components of

physical fitness'.[36] Exercise therapy generally consists of activity of 45 - 60 minutes per session, up to three times per week and prescribed for 10 - 12 weeks.[21]

The mechanism of exercise includes positive feedback from other people, increased sense of self-worth, diversion from negative thoughts, increased social contact and changes in endorphin and monoamine concentrations.[20]

In a Cochrane systematic review of 39 RCTs with moderate quality, exercise was more effective than control in all severity of MDD (SMD= -0.62, 95% CI -0.81 to -0.42).[37, level I] This is supported by another meta-analysis on 13 RCTs of moderate quality (Hedge's g= -0.97, 95% CI -1.40 to -0.54).[38, level I]

Adverse effects of exercise varies which included musculoskeletal pain, chest pain and falls.[37, level I]

v. Relaxation
Relaxation technique is a method to help a person attain a state of calmness.

In a Cochrane systematic review of 15 RCTs, relaxation techniques addressed were progressive muscle relaxation, relaxation imagery, autogenic training, combined or enhanced versions of these, as well as relaxation adjunctive to other treatments. Relaxation reduced self-reported depression (SMD= -0.59, 95% CI -0.94 to -0.24) compared with wait-list, no treatment or minimal treatment post-intervention in MDD. However, when compared with psychological treatment (mainly CBT), it was less effective in reducing self-reported depression (SMD= 0.38, 95% CI 0.14 to 0.62) and showed no difference on clinician-rated depression (SMD=0.29, 95% CI -0.18 to 0.75).[39, level I] The limitation of this review is that the quality of majority of primary papers was not assessed due to inadequate methodological details.

vi. Psychospiritual Intervention
It is crucial to be culturally sensitive in providing mental health care. WHO has declared that spirituality is an important dimension of quality of life.[40] The biopsychosocial and spiritual model[41] is currently being widely used.

Definition of spirituality refers to 'a dimension of human experience related to the transcendent, the sacred, or to ultimate reality and is closely related to values, meaning and purpose in life'. Religion is usually defined as 'systems of beliefs and practices related to the sacred or divine, as held by a community or social group'.[42]

There is no retrievable evidence on psychospiritual intervention specifically on MDD. However, it has been shown to reduce the depressive symptoms in a diverse population.

In a systematic review, all included studies were significantly in favour of faith-adapted CBT in depression outcomes compared with control (range of SMD= -1.20 to -3.07). Faith-adapted CBT is defined as 'integrated faith into established evidence-based treatments by components of discussion of religious or scriptural teachings as supportive evidence to counter irrational thoughts or to support cognitive or behavioural change; use of positive religious and spiritual coping techniques; promotion of helpful belief or value systems or use of shared value systems to strengthen therapeutic relationships and incorporation of religious practices e.g. prayer'.[43, level I]

Another systematic review showed beneficial effects of religious and spiritual interventions in reduction of depressive symptoms between one and six months compared with control (SMD= -0.24 95% CI -0.48 to 0.00). The interventions included religious affiliation of Christians, Muslims, Buddhists and Hindus. The spiritual components included 'teaching spiritual religious principles, client prayer, reading sacred texts and religious imagery or spiritual meditation based on cognitive therapy or CBT, humanistic therapy, non-psychological religious teachings and a combination of these approaches'.[44, level I]

Psychotherapy

Psychotherapy for the treatment of MDD has been shown to reduce psychological distress and improving recovery through the therapeutic relationship between the therapist and the patient.

There is a wide range of psychotherapy available with considerable variation in the robustness of the evidence.[45, level I]

Psychotherapy requires:[20, 30]
- a competent practitioner trained in an evidence-based approach
- a specific method of therapy delivery (e.g. through a manual)
- psychoeducation as an important element of treatment

These interventions are generally time-limited.

A systematic review of 23 RCTs examined the effectiveness of psychotherapy (i.e. behavioural activation, CBT, interpersonal psychotherapy (IPT), problem-solving therapy (PST), psychodynamic therapy, social skills training and supportive counselling) and antidepressants in the treatment of acute MDD. There was no significant difference in response to treatment for combined psychotherapy and antidepressants compared with psychotherapy alone at six months and

≥1 year. However, the combination yielded better treatment response compared with antidepressants alone at:[46, level I]
- ≥6 months (OR=2.93, 95% CI 2.15 to 3.99)
- >1 year (OR=2.23, 95% CI 1.43 to 3.41)

The primary papers in the review were generally of moderate quality with no significant heterogeneity. However, there were possible publication bias noted.

A meta-analysis showed that psychotherapies were more effective than control conditions in:[47, level I]
- after therapy (p=0.002)
- response (p<0.001)
- remission (p=0.011)

The quality of the included primary papers was of low to moderate quality.

In a network meta-analysis, seven psychotherapies (i.e. IPT, behavioural activation, CBT, PST, psychodynamic therapy, social skills therapy and supportive counseling) were more effective than wait-list control condition and showed moderate to large effect sizes (range of Cohen's d= -0.62 to -0.92). In a stepwise restriction of analyses of the same study, there were robust effects for CBT, IPT and PST (Cohen's d=0.46) compared with wait-list. The primary papers included in this review were of moderate quality.[45, level I]

A meta-analysis studied on group psychotherapies which was defined as group intervention based on any form of psychotherapy conducted on ≥3 participants. Group-CBT and TAU was more effective in reducing depressive symptoms in immediate post-treatment (within one week) and medium- to long-term (>3 months) compared with TAU alone with SMD of -0.55 (95% CI -0.78 to -0.32) and -0.47 (95% CI -0.87 to -0.08) respectively. In another analysis, seven RCTs showed individual-CBT was more effective than group CBT immediately post-treatment (SMD=0.38, 95% CI 0.09 to 0.66), but not significant at short-term or medium- to long-term follow-up. No firm conclusion can be made on three other types of group psychotherapy (dialectic behavioural therapy, IPT and self-controlled therapy). However, the primary papers included were of poor quality.[48, level I]

i. Cognitive Behavioural Therapy

CBT focuses on the impact a person's unhelpful thoughts have on the current behavior and functioning, through cognitive restructuring and behavioral approach.

Four meta-analyses of moderate quality primary papers looked at the effectiveness of CBT compared with other treatment in mild to moderate MDD.

- CBT was more effective in reducing depressive symptoms than control (Hedges' g=0.71, 95% CI 0.62 to 0.79; NNT=2).[49, level I]
- CBT combined with pharmacotherapy was more effective in reducing depressive symptoms than pharmacotherapy alone (Hedges' g=0.49, 95% CI 0.20 to 0.69; NNT=3).[49, level I]
- CBT was as effective as pharmacotherapy in reducing depressive symptoms.[49, level I] Similarly, there was no significant difference between CBT and second-generation antidepressants in response and remission.[50, level I]
- CBT was as effective as other psychotherapies (i.e. Supportive Therapy, Behavioural Therapy, psychodynamic psychotherapy, IPT, PST and other psychotherapies) in reducing depressive symptoms.[49, level I]
- CBT combined with antidepressants was as effective as other psychotherapies combined with antidepressants (sub-group analysis).[46, level I]
- Brief CBT (i.e. ≤8 sessions) was more effective than control in reducing symptoms of depression (ES= -0.42, 95%, CI -0.74 to -0.10).[51, level I]

A meta-analysis of 14 RCTs of moderate quality on group psychological therapies plus usual care for MDD was more effective than usual care alone in reducing depressive symptoms at immediate post-treatment and more than three months [SMD= -0.55 (95% CI -0.78 to -0.32) and SMD= -0.47 (95% CI -0.87 to -0.08) respectively]. However, there was no significant difference at short-term follow-up (more than one week to three months).[48, level I]

ii. Interpersonal Psychotherapy

IPT focuses on interpersonal relationship in assisting patients to improve social support network and manage interpersonal distress that may be associated with the depression.

A meta-analysis of 31 studies of moderate quality found that IPT was more effective than control in the treatment of acute MDD (Hedges' g=0.60, 95% CI 0.45 to 0.75; NNT=3). However, there was no significant difference between IPT and antidepressant medication or other psychotherapies.[52, level I]

In the same meta-analysis, combined IPT and antidepressant was more effective than IPT alone (Hedges' g=0.24, 95% CI 0.03 to 0.46; NNT=7). There was no significant difference between combined IPT and antidepressant compared with antidepressant alone.[52, level I]

In a meta-analysis on seven psychotherapeutic interventions for patients with MDD, IPT was significantly more effective than supportive therapy (d= -0.30, 95% CrI -0.54 to -0.05).[45, level I]

iii. Problem-solving Therapy

PST focuses on identifying personal problems, implementing the most adaptive solutions to the problems and evaluating chosen solutions.

In one meta-analysis of 13 RCTs, PST was more effective than control group (waiting list/usual care) in reducing depressive symptoms in MDD (d=0.83, 95% CI 0.45 to 1.21).[53, level I] This is supported by a systematic review of 22 RCTs with similar comparison.[54, level I] Both reviews included moderate quality primary papers.

iv. Behavioural Therapy

Behavioural therapy aims at increasing pleasant and socially reinforcing activities, which can include social skills training, assertiveness training and relaxation therapy.

A Cochrane review of 25 studies of low to moderate quality showed no difference between behavioural therapy and other psychological interventions (i.e. cognitive-behavioural, third wave cognitive-behavioural, psychodynamic, humanistic and integrative therapies) in response rate or drop-out rate in acute MDD.[55, level I]

Behavioural therapy also focuses on behavioural activation (i.e. a behavioural component of CBT). A meta-analysis of 26 RCTs of low to moderate quality primary papers found behavioural therapy to be more effective in reducing depressive symptoms in acute MDD compared with:[56, level I]
- control (Hedges' g= -0.74, 95% CI -0.91 to -0.56; NNT=2)
- antidepressant medication (Hedges' g= -0.42, 95% CI -0.83 to -0.00; NNT=4)

Another meta-analysis found no significant difference between extended behavioural activation and treatment as usual (TAU) in response rate and drop-out rates for acute MDD.[57, level I]

v. Third-wave Cognitive Behavioural Therapy

Two Cochrane systematic reviews compared third wave CBT therapies (i.e. extended behavioural activation, acceptance and commitment therapy and competitive memory training) for acute MDD with control[57, level I] and other psychological therapies.[58, level I]

Third-wave CBT showed better response rate than control (RR=0.51, 95% CI 0.27 to 0.95). There was no significant difference in drop-out rates.[57, level I] In another comparison, there was no significant difference between third-wave CBT and other psychological therapies in response rate and drop-out rates.[58, level I]

The primary papers included in the two reviews were of very low quality.[57 - 58, level I]

vi. Psychodynamic Psychotherapy

Psychodynamic psychotherapy focuses on past unresolved conflicts and relationships, and the impact they have on current situation. The active exploration of the patient's life and emotions distinguish psychodynamic psychotherapy from psychoanalytic psychotherapy. The main element distinguishing short-term psychodynamic psychotherapy (STPP) from long-term psychodynamic treatment is time-restriction.

In a subgroup analysis from a Cochrane systematic review, STPP reduced depressive symptoms compared with TAU or wait-list at short-term follow-up in MDD (SMD= -0.47, 95% CI -0.67 to -0.28). The effect did not reach statistical significance at medium- and long-term follow-up. [59, level I] This is supported by another meta-analysis when STPP was more effective than control condition at post-treatment of MDD (d=0.61, 95% CI 0.33 to 0.88, NNT=2).[60, level I]

An RCT of CBT vs STPP showed no significant difference in remission rate.[215, level I]

vii. Marital Therapy

Marital therapy aims at modifying negative interactional patterns and increasing mutually supportive aspects of couple relationships.

A Cochrane systematic review on eight trials of moderate quality found marital therapy was more effective in reducing marital distress (SMD= -0.94, 95% CI -1.38 to -0.50) compared with individual psychotherapy in outpatients and community patients with MDD. Marital therapy showed no significant difference compared with individual psychotherapy in improving depressive symptoms or reducing persistence of depression.[61, level I]

viii. Internet- and Mobile/Computer-based Interventions

Internet- and mobile/computer-based interventions are any psychotherapeutic programmes provided in an online or mobile/computer setting. These interventions are considered as low intensity psychotherapy as it can be self-guided and may be facilitated by a competent practitioner.[20] A meta-analysis of moderate quality primary papers showed such interventions reduced depressive symptoms compared with wait-list conditions at 4 - 12 weeks (Hedges' g= -0.90, 95% CI -1.07 to -0.73) in MDD. Anxiety symptoms were also reduced (Hedges' g= -0.41, 95% CI -0.69 to -0.12).[62, level I]

Based on another meta-analysis of 14 studies, internet-based CBT (iCBT) was effective in reducing symptoms of depression post-treatment compared with control up to six months follow-up only (SMD= -0.48, 95% IC -0.63 to -0.33). Nonetheless, iCBT had significantly

higher drop-out rate in MDD. In this meta-analysis, there was no quality assessment reported but publication bias was significant.[63, level I]

In a meta-analysis of individual participant data of 3876 participants (high methodological quality primary papers), self-guided iCBT was more effective than control on depressive symptoms severity (Hedges' g=0.27, 95% CI 0.17 to 0.37) and treatment response (OR=1.95, 95% CI 1.52 to 2.50) in mild to moderate MDD. It yielded a corresponding NNT of 8. Adherence to the treatment was significantly associated with lower depressive symptoms and better response to treatment.[214, level I]

> **Recommendation 4**
> • In mild to moderate major depressive disorder, psychosocial intervention and psychotherapy should be offered, based on resource availability, but not restricted to the following:
>   ○ cognitive behavioural therapy
>   ○ interpersonal therapy
>   ○ problem-solving therapy
>   ○ behavioural therapy
>   ○ internet-based cognitive behavioural therapy

> • The type of psychotherapy offered to patients will depend on various factors including:
>   ○ patient preference and attitude
>   ○ nature of depression and its complexities
>   ○ availability of trained therapist
>   ○ therapeutic alliance
>   ○ availability of therapy

B.   Pharmacotherapy

The aim of pharmacotherapy in the acute phase of MDD is to achieve symptom remission between 8 - 12 weeks. Early improvement (defined as >20% - 30% improvement from baseline depression scores at 2 - 4 weeks) predicts response and remission at 6 to 12 weeks.[27]

In mild to moderate MDD, patients should be offered psychosocial/ psychological interventions. However, the doctor may choose to start antidepressant medication as an initial measure in situations e.g.:
   • past history of moderate to severe depression[21]
   • patient's preference[27]
   • previous response to antidepressants[27]
   • lack of response to non-pharmacotherapy interventions[27]
Patients should be closely monitored and given a follow-up appointment within two weeks.[21]

4.1.2 Moderate to Severe

A. Psychological and Psychosocial Interventions

In a meta-analysis of 22 RCTs of moderate quality, combined pharmacotherapy with psychotherapy had higher probability of remission at 2, 3, 4, 6 and 12 months, with the highest effect shown at four months (OR=2.36, 95% CI 1.58 to 3.55), compared with pharmacotherapy alone in moderate to severe MDD. This combination also showed lower risk of relapse if continued into the continuation phase (OR=3.28, 95% CI 1.76 to 6.09).[64, level I]

Recommendation 5
• In moderate to severe major depressive disorder, a combination of pharmacotherapy and psychotherapy should be offered.

Exercise was shown to be more effective than control across severity in MDD.[37, level I]

Recommendation 6
• In moderate to severe major depressive disorder, exercise may be offered as an adjunct treatment.

B. Pharmacotherapy

Pharmacotherapy is the mainstay of treatment for moderate to severe depression. There are many classes of antidepressants available e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), monoamine oxidase inhibitors (MAOIs), noradrenaline and dopamine reuptake inhibitors (NDRIs) and tricyclic antidepressants (TCAs). The newer ones are multimodal antidepressant and melatonergic agonist and serotonergic antagonist. There are other agents that have shown emerging evidence in special conditions related to depression.

Choice of Antidepressant Medication
• The choice of antidepressant medication will depend on various factors including efficacy and tolerability, patient profile and comorbidities, concomitant medications and drug-drug interactions, cost and availability, as well as patients' preference.
• Taking into account efficacy and side-effect profiles, most second-generation antidepressants namely SSRIs, SNRIs, NaSSAs, melatonergic agonist & serotonergic antagonist, NDRIs and multimodal antidepressant may be considered as the initial treatment medication, while the older antidepressants such as TCAs and MAOIs are considered for subsequent choice later.

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i.   Selective Serotonin Reuptake Inhibitors

There are six meta-analyses on the effectiveness of SSRIs in treating moderate to severe depression. However, the risk of bias in primary papers of some of the meta-analyses resulted in caution in interpretation of the results.

In a recent meta-analysis, SSRIs were more effective than placebo in reducing HDRS scores (MD= -1.94, 95% CI -2.50 to -1.37) and decreasing risk of no remission (RR=0.88, 95% CI 0.84 to 0.91) in MDD.[65, level I]

Other meta-analyses on treatment response with SSRIs in acute MDD showed that:
- sertraline was more effective than fluoxetine (OR=0.73, 95% CI 0.59 to 0.92)[66, level I]
- escitalopram was more effective than citalopram (OR=0.67, 95% CI 0.50 to 0.89)[67, level I]
- fluoxetine and paroxetine were equally effective (OR=1.03, 95% CI 0.88 to 1.20) and tolerable (OR=0.95, 95% CI 0.81 to 1.12) [68, level I]

A meta-analysis demonstrated that SSRIs as a group were less effective than SNRIs for remission in MDD (OR= 1.27, 95%CI 1.06 to 1.52).[69, level I] However, sertraline and escitalopram individually was as effective as SNRIs.[66 - 67, level I]

In another meta-analysis, although SSRIs had lower rates of remission in MDD compared with mirtazapine (p=0.0006), it had lower overall drop-out rates (p=0.0265) after six weeks of treatment.[70, level I]

In terms of adverse event, SSRIs:
- had increased risk of adverse events compared with placebo [65, level I]
- lower dropout rates due to ADRs compared with SNRIs (p<0.001) [69, level I]

Apart from that, sertraline in MDD had:[66, level I]
- less side effects compared with paroxetine (OR=0.28, 95% CI 0.08 to 0.96)
- less adverse events compared with amitriptyline (OR=0.59, 95% CI 0.39 to 0.89) and imipramine (OR=0.17, 95% CI 0.09 to 0.32)
- higher adverse events compared with escitalopram (OR 1.76, 95% CI 1.06 to 2.94)

In a cohort study, SSRI-treated patients did not have higher suicide attempts compared with untreated patients (HR=0.65, 95% CI 0.14 to 3.02), and with SNRI-treated patients (HR=0.76, 95% CI 0.36 to 1.63) in MDD.[71, level II-2]

ii.   Serotonin Noradrenaline Reuptake Inhibitors

In a meta-analysis of high quality RCTs, venlafaxine was more effective in response rate than SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), but showed no difference with duloxetine and TCAs (amitriptyline, clomipramine, dosulepine, imipramine, maprotiline and nortriptyline) in moderate to severe MDD. However, duloxetine had no difference in response rate compared with SSRI.[72, level I]

In the same meta-analysis, there was no significant difference between duloxetine or venlafaxine and SSRIs in remission rate based on Hamilton Depression Rating Scale (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS). There was also no significant difference between venlafaxine and TCAs.[72, level I] Another meta-analysis found, SNRIs as a group (venlafaxine and duloxetine) were more effective than SSRIs (fluoxetine, paroxetine and sertraline) in achieving remission in moderate to severe MDD at 8 - 12 weeks (OR= 1.27, 95% CI 1.06 to 1.52).[69, level I]

In another meta-analysis, desvenlafaxine was significantly more effective in both response and remission rate compared with placebo and antidepressants in general (i.e. venlafaxine, duloxetine or escitalopram).[73, level I]

Adverse events were:
- higher in duloxetine compared with venlafaxine (OR=1.79, 95% CI 1.16 to 2.78)[72, level I]
- higher in duloxetine and venlafaxine compared with SSRIs [OR=1.38 (95% CI 1.15 to 1.66) and OR=1.53 (95% CI 1.10 to 2.13) respectively][69, level I; 72, level I]
- non-significantly differed between venlafaxine and TCAs (OR=0.97, 95% CI 0.67 to 1.41)[72, level I]

There was high discontinuation rate in desvenlafaxine compared with placebo (RR=1.98, 95 % CI 1.45 to 2.69).[73, level I]

iii.   Noradrenergic & Specific Serotonergic Antidepressants

In a large Cochrane systematic review of 29 RCTs, mirtazapine was significantly more effective than SSRIs and SNRIs in term of response and remission at two weeks, and response at 6 - 12 weeks. When compared with TCAs, there was no difference in term of response at two weeks and 6 - 12 weeks.[74, level I]

Mirtazapine is one of the first-line antidepressants and more effective compared with duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine. It has minimal or low potential for drug-drug interaction. It is also one of the antidepressants that can be used for MDD with sleep disturbances.[27]

In the same review, mirtazapine was significantly less likely than SSRI to cause gastrointestinal (GI) symptoms, sweating, sexual dysfunction, tremor and sleep disturbances. It was also significantly less likely than SNRI to cause sleep disturbance, sweating and constipation. Apart from this, it was significantly less likely than TCAs to cause hypertension/tachycardia and tremor.[75, level I]

Mirtazapine was significantly more likely than SSRIs to cause more weight gain, increase salivation, fatigue and sleepiness. It was significantly more likely than SNRIs to cause fatigue.[75, level I]

iv.   Melatonergic Agonist & Serotonergic Antagonist
At present, agomelatine is a melatonin MT1 and MT2 agonist, and a $5HT_{2c}$ antagonist used in depression. It had higher response rate compared with placebo (RR=1.25, 95% CI 1.11 to1.41) and sertraline (SMD=0.23, 95%, CI 0.01 to 0.46) in MDD.[77, level I] In a Cochrane systematic review of 13 RCTs, agomelatine showed no significant difference in response and remission rates in MDD when compared with SSRIs (paroxetine, fluoxetine, sertraline, escitalopram) and SNRI (venlafaxine).[78, level I]

Agomelatine in MDD had less side effects including sexual dysfunction compared with other SSRIs (paroxetine, fluoxetine, sertraline, escitalopram) (RR=0.91, 95% CI 0.84 to 0.98).[78, level I]

Agomelatine showed lower drop-out rate due to side effects compared with other antidepressants agents (escitalopram, fluoxetine, sertraline, paroxetine and venlafaxine) (RR = 0.61, 95% CI 0.48 to 0.78) in MDD.[77, level I]

Agomelatine were reported to cause elevated liver enzymes but serious hepatic reactions were rare. Liver function test is required at approximate three, six, 12 and 24 weeks after initiation dosage, after dosage increment or when clinically indicated.[79, level I]

v.   Multimodal Serotonin Modulator
Vortioxetine is a multimodal serotonin modulator. Three meta-analyses showed that vortioxetine was significantly more effective than placebo in terms of response and remission for acute treatment of MDD.[80 - 82, level I] This is supported by a recent network meta-analysis which found that vortioxetine was more effective in response compared with placebo for acute MDD (OR=1.66, 95% CI 1.45 to 1.92).[83, level I]

In a Cochrane systematic review, vortioxetine was less effective compared with duloxetine for response (RR=0.86, 95% CI 0.79 to 0.94) and reduction of depressive symptoms (MD=1.99, 95% CI 1.15 to 2.83) in adults with acute MDD. The same systematic review showed no

significant differences between vortioxetine and venlafaxine for similar outcomes.[80, level I] An earlier meta-analysis showed that vortioxetine was less effective at doses of 5 mg (RR=0.88, 95% CI 0.80 to 0.98), 15 mg (RR=0.78, 95% CI 0.68 to 0.90) and 20 mg (RR=0.82, 95% CI 0.72 to 0.94) for response, but had no significant differences for remission compared with SNRIs in adults with acute MDD.[81, level I]

Although vortioxetine caused more adverse events (e.g. nausea, vomiting and hyperhidrosis) compared with placebo, it had less adverse events compared with venlafaxine or duloxetine.[80 - 81, level I]

CANMAT recommends vortioxetine for MDD with cognitive dysfunction.[27]

vi. Tricyclic Antidepressants
TCAs have been used for long time compared with other classes of antidepressants. There is scarcity of new evidence of TCAs since the previous edition of the CPG. A Cochrane systematic review in 2012 showed that amitriptyline was more effective than placebo in the acute phase of MDD (OR=2.64, 95%CI 2.28 to 3.06). The side effects e.g. sexual dysfunction, weight gain, urination problems, dyspepsia, tremor, sedation, tachycardia, dizziness, nervousness and fatigue were significantly higher in amitriptyline. Apart from that, amitriptyline had also significantly higher anticholinergic side effects e.g. dry mouth, constipation and visual disturbances.[84, level I]

vii. Noradrenaline/Dopamine Reuptake Inhibitor
Bupropion is a noradrenaline/dopamine-reuptake inhibitor. A meta-analysis of five RCTs showed that bupropion was more effective than placebo in reducing depression scores in acute phase MDD in adults (Hedge's g= -2.02, 95% CI -2.93 to -1.11).[85, level I] However, quality assessment of primary papers was not addressed and there was significant heterogeneity among the papers. A recent network meta-analysis showed that bupropion was more effective than placebo for response in acute MDD (OR=1.58, 95% CI 1.35 to 1.86).[83, level I]

A meta-analysis found that bupropion was as effective as venlafaxine for response, remission, and reduction of depression scores in MDD. There was no significant difference between bupropion and venlafaxine in terms of Changes in Sexual Functioning Questionnaire scores and adverse events.[86, level I]

viii. Monoamine Oxidase Inhibitors
Although MAOIs are efficacious in treatment of MDD, they are not recommended as first-line treatment due to their poor tolerability profile, increased side-effects, and serious drug interactions.[27, 29]

- Based on a recent network meta-analysis on moderate to severe acute MDD in adults:[83, level I]
  - all antidepressants were more effective than placebo in response
  - agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine and vortioxetine were more effective than other antidepressants whereas fluoxetine, fluvoxamine, reboxetine and trazodone were the least effective drugs
  - as for acceptability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline and vortioxetine were more tolerable than other antidepressants whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone and venlafaxine had the highest dropout rates

Recommendation 7
- In moderate to severe major depressive disorder, one of the second-generation antidepressants should be prescribed:
  - selective serotonin reuptake inhibitors
  - serotonin noradrenaline reuptake inhibitors
  - noradrenergic and specific serotonergic antidepressants
  - melatonergic agonist and serotonergic antagonist
  - multimodal serotonin modulator
  - noradrenaline/dopamine-reuptake inhibitor

ix. Benzodiazepines

In the management of MDD, combination of certain class of drugs may be required. In a Cochrane systematic review of 10 RCTs, a combination of benzodiazepines and antidepressants was significantly more effective only at 1 - 4 weeks compared with antidepressants alone based on HAM-D and Comprehensive Psychiatric Rating Scale Visual Analog Scale.[87, level I]

However, the combination therapies significantly caused more side effects e.g. drowsiness/sedation compared with antidepressant alone (RR=0.56, 95% CI 0.34 to 0.91).[87, level I]

Existing guidelines recommend benzodiazepines may be considered for patients with anxiety, insomnia and/or agitation problem in MDD but may be used **no longer than 2 - 4 weeks** to avoid dependency.[20, 21, 88]

> **Recommendation 8**
> • Benzodiazepines may be used as an adjunct to antidepressant treatment in major depressive disorder with anxiety, agitation or insomnia.
>   ○ Avoid prescribing for more than 2 - 4 weeks due to risk of dependency.

x.   Non-benzodiazepine Hypnotics

A group of selective gamma-aminobutyric acid agonist/non-benzodiazepine hypnotics (i.e. zolpidem and eszopiclone) might be useful for short-term treatment of sleep disturbance in patients with MDD.

A meta-analysis of six RCTs found that non-benzodiazepines as an adjunctive therapy with antidepressants was significantly more effective in achieving remission rates compared with placebo and antidepressants alone, but showed no significant difference in response rate. There was no significant difference in adverse events between the two groups.[89, level I]

xi.   Emerging Pharmacotherapy Interventions
•   Psychostimulants

Psychostimulants have been used as part of the treatment in MDD due to their mood elevating effects. However, a Cochrane systematic review showed no difference in it reducing depressive symptoms when used as adjunctive treatment to antidepressants compared with placebo. There was also no difference between psychostimulants as monotherapy or adjunct therapy compared with placebo for response rate in MDD. The limitation of this paper was the primary papers used in this review were old and of poor quality.[90, level I]

Existing guidelines do not recommend the use of psychostimulants in MDD.[20; 29] It may be used as adjunct therapy based on poor evidence.[27]

In a recent systematic review of 22 RCTs where risk of bias was not reported, psychostimulants were more effective in terms of response compared with placebo in MDD (OR=1.41, 95% CI 1.13 to 1.78).[91, level I]

> • There is insufficient evidence to suggest the use of psychostimulants in MDD.

•   Ketamine

In a Cochrane systematic review of nine RCTs, patients with mainly moderate to severe MDD in acute phase who received intravenous (IV) ketamine had significantly greater improvement in both response and

remission rate compared with placebo within 24 hours, 72 hours and one week but not at two weeks of administration.[92, level I]

The main adverse events of IV ketamine were confusion and emotional blunting.[92, level I] Meanwhile, a recent systematic review of high quality RCTs had categorised the side effects of mainly IV ketamine into common, less common and major groups (refer to **Table 1**).[93, level I]

Table 1. Category of side effects of ketamine

Categories	Side Effects
Common	• Anxiety • Agitation or irritability • Euphoria or mood elevation • Delusion or unusual thought • Panic • Apathy
Less common	• Feeling of detachment • Emotional blunting • Psychosis • Emotional lability • Craving attention • Formal thought disorder
Major	• Urological side effects e.g. cystitis, bladder dysfunction • Hepatic side effects • Craving or dependence • Cognitive changes

There was no significant difference in drop-out rate between ketamine and placebo in MDD.[92, level I]

Recommendation 9
• Intravenous ketamine maybe considered for short-term (not more than two weeks) in acute phase of moderate to severe major depressive disorder.

4.2 Continuation and Maintenance Phase
4.2.1 Psychosocial Intervention and Psychotherapy
A meta-analysis showed that psychological interventions reduced the risk of relapse or recurrence in MDD compared with:[94, level I]
   • TAU (RR=0.64, 95% CI 0.53 to 0.76; NNT=5). The effect during the continuation and maintenance phase was better when it included treatment during acute phase (p=0.005)
   • antidepressants with/without TAU (RR=0.83, 95% CI 0.70 to 0.97; NNT=13)
However, the primary papers included were of low quality.

i.   Cognitive Behavioural Therapy

In MDD, CBT was effective in reducing the risk of relapse or recurrence compared with TAU (RR=0.68, 95% CI 0.54 to 0.87; NNT of 5) but showed no significant difference when compared with antidepressants.[94, level I]

ii.   Mindfulness-based Cognitive Therapy

In MDD, mindfulness-based cognitive therapy (MBCT) was effective in reducing the risk of relapse or recurrence compared with TAU (RR=0.66, 95% CI 0.53 to 0.82; NNT of 4) but showed no significant difference when compared with antidepressants.[94, level I]

A good RCT found no significant difference between MBCT with support to taper or discontinue antidepressants and maintenance antidepressants alone over 24 months in maintenance phase of MDD.[95, level I]

In an RCT on treatment resistant depression (TRD), as an adjunct to pharmacotherapy, MBCT was more effective than Health Education Programme in reducing depressive symptoms (p=0.01) and improving treatment responders (p=0.03) at eight weeks. However, no difference was found on rates of remission (p=0.15).[96, level I]

iii.   Interpersonal Therapy

IPT was effective in reducing the risk of relapse or recurrence in MDD compared with TAU (RR=0.41, 95% CI 0.27 to 0.63; NNT of 6) but showed no significant difference when compared with antidepressants.[94, level I]

4.2.2   Pharmacotherapy

The aim of pharmacotherapy in maintenance phase is to prevent relapse and recurrence. The duration of maintenance phase treatment is between six to nine months after remission. However, consider maintenance treatment for ≥2 years if there is a high risk of relapse and recurrence as shown below.[27]

> The risks of relapse and recurrence of MDD are as follows:[27]
> * frequent, recurrent episodes
> * severe episodes (psychosis, severe impairment, suicidality)
> * chronic episodes
> * presence of comorbid psychiatric or other medical conditions
> * presence of residual symptoms
> * difficult-to-treat episodes

A meta-analysis of 23 RCTs of moderate quality demonstrated that second-generation antidepressants were more effective than placebo in continuation/maintenance phase of MDD in preventing:[97, level I]
* relapse over eight months (NNT=5, 95% CI 4 to 6)
* recurrence over 16 months (NNT=5, 95% CI 4 to 6)

There was no significant difference in adverse events between antidepressants and placebo during the continuation/maintenance phase treatment of MDD.[97, level I]

Recommendation 10
• Antidepressants should be continued for at least six to nine months after remission and at least two years if there is a high risk of relapse and recurrence.

4.3   Discontinuation of Pharmacotherapy

Discontinuation of antidepressants may be initiated by the doctor or the patient. The patient may experience discomfort when discontinuation is not properly done. The more common discontinuation symptoms in SSRIs include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances and hyperarousal (FINISH acronym). These symptoms could be misunderstood as symptoms of the relapse of MDD. It is estimated that 40% of those who undergo sudden termination of antidepressant develop these symptoms which are self-limiting in 1 - 2 weeks. Discontinuation symptoms are more closely associated with antidepressant of shorter half-life e.g. paroxetine and least likely associated with those of long half-life e.g. fluoxetine.[27] Therefore, discontinuation of antidepressant should be done gradually within weeks or even months unless there is urgency to do it e.g. intolerable side effects.

4.4   Major Depressive Disorder with Psychosis
4.4.1   Pharmacotherapy
MDD with psychotic features or psychotic depression is a serious condition that requires immediate treatment and close monitoring intervention.

A Cochrane systematic review of 12 RCTs of moderate quality showed that the combination of antidepressant and antipsychotic, mostly atypical antipsychotics (AAPs), in response were more effective than placebo, antidepressant or antipsychotic monotherapy:[98, level I]
   • combination vs placebo (RR=1.86, 95% CI 1.23 to 2.82)
   • combination vs antipsychotic (RR=1.83, 95% CI 1.40 to 2.38)
   • combination vs antidepressant (RR=1.70, 95% CI 1.19 to 12.43)
Existing guidelines recommend combination treatment of an antipsychotic and an antidepressant medication than either monotherapies for better response.[20, 99]

> **Recommendation 11**
> • Combination of antidepressant and antipsychotic should be considered in major depressive disorder with psychotic features.

4.4.2 Physical Treatment

A Cochrane systematic review of 16 RCTs showed electroconvulsive therapy (ECT) was more effective than repetitive transcranial magnetic stimulation (rTMS) in MDD with psychosis after two weeks of treatment (SMD=7.90, 95% CI 1.98 to 13.82).[100, level I]

ECT may be considered in psychotic depression.[21]

> **Recommendation 12**
> • Electroconvulsive therapy may be considered in major depressive disorder with psychotic features.

4.5 Failed Response to Initial Treatment

Approximately 20 - 30% of people with MDD do not respond satisfactorily to the usual recommended dose of antidepressants and approximately 15% may develop chronic depression. Treatment failure can be due to a number of factors:[21]
- incorrect diagnosis (e.g. failure to diagnose bipolar disorder)
- psychotic depression
- organic conditions e.g. anaemia or hypothyroidism
- co-morbid psychiatric disorder e.g. substance abuse or dependence, panic disorder, obsessive-compulsive disorder and personality disorder
- adverse psychosocial factors
- non/poor compliance

These strategies can be used in cases of failure or inadequate response to initial treatment:
- optimisation (refers to increasing the dose of antidepressant to the standard maximum dose for 6 - 12 weeks)[101, level III]
- switching (refers to a change from one antidepressant to another)
- combination
- augmentation

In patients who fail to show response to initial treatment, optimisation is recommended rather than switching as because of wide inter-individual variation in dosage and there was no clear dose-response relationship for most antidepressants.[21] CANMAT guidelines for MDD also recommends optimising the antidepressant dose for patients who do

not improve at week two to week four if the medication can be tolerated. However, if tolerability is an issue, switching to another antidepressant should be done.[27]

An RCT on chronic or recurrent MDD showed no significant difference in response and remission between escitalopram (up to 20 mg/day) plus placebo, sustained-release bupropion (up to 400 mg/day) plus escitalopram (up to 20 mg/day), and extended-release venlafaxine (up to 300 mg/day) plus mirtazapine (up to 45 mg/day) at 12 weeks and seven months treatment.[102, level I]

NICE does not recommend augmentation with thyroid hormones as a routine strategy due to inconsistent evidence of effectiveness in MDD patients with inadequate response.[20]

> **Recommendation 13**
> • Optimisation of antidepressant should be considered in patients who show inadequate response to initial treatment in major depressive disorder.
>   ○ If optimisation fails, refer to a psychiatrist for switching/combination/ augmentation options.

4.6 Next-Step Treatment/Treatment-Resistant Depression

There is a lack of consensus on the concept and definition of TRD.[27] TRD has been defined as failure to respond to two or more antidepressants at an adequate dose for an adequate duration, given sequentially.[21] Adequate duration refers to at least four weeks and adequate dose refers to at least 150 mg/day of imipramine equivalent. However, the use of this criteria has been debated because the definition does not take into account adjunctive strategies and differentiate partial responders with non-responders.[27] The updated NICE guidelines for MDD has also combined their previous sections on acute-phase non-responders and TRD under 'next-step treatments'.[20] Due to these reasons, the DG CPG considers similar approach.

The following strategies can be used in the next-step treatments:
  • switching
  • augmentation (refers to the addition of a non-antidepressant to an ongoing antidepressant)
  • combination therapy (refers to the addition of another antidepressant to the ongoing antidepressant)
  • physical treatment
  • psychotherapy as an adjunct

4.6.1 Switching

In a meta-analysis comparing within vs across-class switches in SSRI-resistant depression, a higher remission rates were observed when the SSRI antidepressant was switched to a non-SSRI (bupropion, mirtazapine, venlafaxine) than an SSRI antidepressant (citalopram, paroxetine, sertraline) with the pooled RR for remission of 1.29 (95% CI 1.07 to 1.56).[103, level I]

4.6.2 Combination

There has been lack of research on combination of antidepressants for TRD. In a phase III RCT of mirtazapine added to SSRIs or SNRIs for TRD, there were no significant differences observed in depressive symptoms at 24 weeks and 52 weeks between the combination and placebo added to SSRIs or SNRIs. There was also no significant difference in side effects at 12 weeks between the two groups.[104, level I]

In the previous edition of CPG on MDD, combination of an antidepressant with another antidepressant may be considered in patients with TRD. Particular care should be taken to monitor for adverse events.[21]

4.6.3 Augmentation
•   **Augmentation with Atypical Antipsychotics**
A meta-analysis on TRD showed that AAPs (olanzapine, risperidone, quetiapine and aripiprazole) augmentation had higher overall response and remission rates compared with placebo [OR=1.69 (95% CI 1.46 to 1.95) and OR=2.00 (95% CI 1.69 to 2.37) respectively]. Mean ORs did not differ among the AAPs and were not affected by trial duration or method of establishing treatment resistance. However, quality assessment of primary studies was not reported.[105, level I] This is supported by a network meta-analysis where the same adjunctive AAPs were significantly more effective in remission rates compared with placebo in TRD (OR ranged from 1.79 to 2.17).[106, level I]

Discontinuation rates for adverse events were higher for AAPs than for placebo (OR=3.91, 95% CI 2.68 to 5.72).[105, level I]

•   **Augmentation with Lithium**
A meta-analysis showed lithium augmentation with any antidepressants were more effective in response compared with placebo augmentation in TRD (OR=2.89, 95% CI 1.65 to 5.05). Discontinuation due to adverse events did not differ between the two groups.[107, level I] In another meta-analysis on TRD, lithium augmentation with SSRI showed no significant difference with AAP augmentation with SSRI.[108, level I]

•   **Augmentation with Antiepileptic Agents**
A network meta-analysis of seven augmentation agents found no significant difference in effectiveness between antiepileptic agents

(valproate, lamotrigine and carbamazepine) and others (lithium, TCAs, AAPs, buspirone, CBT and tri-iodothyronine).[109, level I]

• **Augmentation with Esketamine**
An RCT showed that antidepressant plus intranasal esketamine was significantly more effective in reducing symptoms of MDD at 4 - 24 hours and improvement of suicidal thought up to 4 hours of administration compared with standard care treatment plus placebo.[110, level I] In 2019, the United States Food and Drug Administration has approved esketamine nasal spray in conjunction with an oral antidepressant as a therapy for patients with TRD.

At the time of writing, there is an on-going multicentre RCT on intranasal esketamine in TRD.

4.6.4 Physical Treatment
In a meta-analysis, ECT plus antidepressant (RR=1.82, 95% CI 1.55 to 2.14) and ECT alone (RR=2.24, 95% CI 1.51 to 3.33) was more effective in response rate compared with antidepressant alone. However, an indirect comparison found no significant difference in the response rate between ECT plus antidepressant and ECT alone. ECT plus antidepressant increased the incidence of memory deterioration relative to ECT alone in the fourth week of treatment.[111, level I]

A recent HTA found that ECT was more effective for both response (RR=1.72, 95% CI 0.95 to 3.11) and remission (RR=1.44, 95% CI 0.64 to 3.23) compared with rTMS in TRD. However, it caused more cognitive impairment compared with rTMS in TRD (p= 0.07).[112, level I]

4.6.5 Psychotherapy
There is limited evidence on psychotherapy for TRD. In an RCT, CBT as an adjunct to pharmacotherapy reduced depressive symptoms in TRD patients in primary care (not responded to at least six weeks treatment with an antidepressant) with a NNT of 4 (95% CI 3 to 6).[113, level I]

In another RCT, there was no significant difference in improvement of depressive symptoms between brief supportive psychotherapy plus medication, cognitive behavioural analysis system of psychotherapy plus medication compared with medication alone in TRD patients.[114, level I]

Recommendation 14
• In treatment resistant depression, the following strategies may be considered:
  ○ switching antidepressants to a different class
  ○ combination of antidepressants
  ○ augmentation with atypical antipsychotics, lithium or antiepileptic agents

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5. PHYSICAL TREATMENT

Physical treatments are non-invasive techniques using electrical or magnetic stimulation targeting specific regions of the brain. Most of these treatments have been studied and are used in patients with TRD who have failed to respond to standard treatments.[115]

There are several types of physical treatments e.g. ECT, rTMS and transcranial direct current stimulation (tDCS).

5.1 Electroconvulsive Therapy

ECT is a therapeutic procedure that induces seizure by applying an electrical stimulus to the brain.

ECT is an established physical treatment in MDD. It is significantly more effective than sham/simulated ECT or placebo in MDD.[20]

In a cohort study, 84.21% of pregnant patients with MDD achieved a complete response (CGI-S score ≤2) with ECT.[116, level II-2]

Compared with rTMS,
- ECT is more effective in response (ARR=36%, 95% CI 14% to 58%) and remission (HAM-D ≤8, p=0.006) in acute treatment of MDD.[117, level I]
- ECT is more effective in MDD with psychosis after two weeks of treatment (SMD=7.90, 95% CI 1.98 to 13.82).[100, level I]
- ECT is significantly more effective for both response (RR=1.72, 95% CI 0.95 to 3.11) and remission (RR=1.44, 95% CI 0.64 to 3.23) in treatment-resistant MDD.[112, level I]

There is no absolute contraindication for ECT.[21] However, the relative contraindications are:[115]
- cerebral space-occupying lesion
- increased intracranial pressure
- recent cerebral haemorrhage
- recent myocardial infarction
- vascular aneurysm or malformation
- pheochromocytoma
- class four or five anaesthesia risk

The side-effects of ECT are mainly cognitive impairments that include short-term retrograde amnesia and anterograde amnesia, and a transient postictal confusional state. Risk of cognitive impairment is lesser in:
- unilateral ECT vs bilateral ECT
- lower dose vs higher dose ECT
- twice a week vs thrice a week ECT

Other side-effects of ECT include headache, muscle soreness and nausea. Serious complications like status epilepticus and laryngospasm can occur.[21]

ECT has lesser side effects in acute treatment (p=0.02)[117, level I] but causes more cognitive impairment compared with rTMS in MDD (p= 0.07).[112, level I]

Although maintenance ECT helps to sustain symptom reduction and reduce hospitalisation rates in chronic TRD, there is little evidence to show that it is more beneficial than pharmacotherapy.[21]

- ECT is indicated in MDD with:[21, 115]
  - acute suicidal ideation
  - high degree of symptom severity and functional impairment
  - psychotic symptoms/features
  - catatonic features
  - rapidly deteriorating physical status e.g. refusal to eat
  - TRD
  - repeated medication intolerance
  - previous favourable response to ECT
  - pregnancy, for any of the above indications
  - patient's preference

Recommendation 15
- Electroconvulsive therapy may be considered in major depressive disorder with*:
  - life-threatening conditions e.g. refusal to eat and high suicidality
  - moderate to severe symptoms for rapid improvement in the acute treatment
  - treatment-resistant depression

*Refer to clinical indications in preceding yellow box.

5.2   Repetitive Transcranial Magnetic Stimulation

rTMS uses powerful and focused magnetic field pulses to induce electrical currents in neural tissue through an inductor coil placed against the scalp. No anaesthesia is required for this procedure. According to standard protocols, rTMS is delivered once daily, five days/week. Thrice weekly stimulation has been reported as effective as five days/week but with slower improvement and require similar number of sessions.[115]

A Cochrane systematic review of 16 RCTs showed no difference between rTMS and sham rTMS in severe MDD except for one time

period (after two weeks of treatment).[100, level I] A recent HTA found that rTMS was more significantly effective in response and remission than sham rTMS in treatment-resistant MDD.[112, level I]

rTMS caused more adverse events e.g. headache, scalp discomfort, GI problems and vertigo than sham.[112, level I]

For comparison with ECT, refer to **Subchapter 5.1** on **ECT**.

5.3 Transcranial Direct Current Stimulation

tDCS delivers a continuous low-amplitude electrical current to a specified cortical region of the brain using scalp electrodes. Repeated use of tDCS may lead to neuroplasticity effects which are mediated via N-methyl-D-aspartate receptor-dependent mechanisms.[115]

Two meta-analyses demonstrated that tDCS was significantly more effective in treating moderate to severe MDD than sham. However, those with history of treatment resistance had poorer response to tDCS.[118 - 119, level I]

6. COMPLEMENTARY AND ALTERNATIVE TREATMENT

Complementary and alternative medicine (CAM) is broadly defined as "a group of diverse medical and health care systems, practices and products that are not generally considered part of conventional medicine". Although 10% to 30% of depressed patients are thought to use CAM treatments, there is generally no medical supervision and these treatments are often used in combination with existing medications without considering possible interactions.[120]

i.   St John's wort (Hypericum extracts)
In a Cochrane systematic review of 29 trials, hypericum was significantly more effective than placebo in the treatment of moderate to severe MDD. It was found to be as effective as tri- or tetracyclic antidepressants and SSRIs in MDD.[121, level I]

In terms of adverse effects, there was no significant difference in the number of patients dropping out for adverse effects between hypericum extracts and placebo. It also significantly caused less adverse effects compared with older antidepressants or SSRIs.[121, level I] The main side effects of hypericum extracts are headache, dryness of mouth, nausea, GI symptoms and sleepiness.[21]

Although there is evidence that hypericum is more effective than placebo and better tolerated than standard antidepressant for the treatment of major depressive disorder, there are uncertainty about appropriate doses, variation in the nature of preparations and potentially serious drug interactions.[21]

> • The issues on appropriate doses, variation in the nature of preparations and potentially serious drug interactions of hypericum is yet to be established before it can be recommended.

ii.   Acupuncture
A large Cochrane systematic review of 30 trials showed insufficient evidence of a consistent beneficial effect of acupuncture compared with a wait-list control, sham acupuncture control or medication in mild to severe MDD. A subgroup analysis showed patients with stroke experienced a reduction in depression with manual acupuncture compared with SSRIs (RR=1.66, 95% CI 1.03 to 2.68).[122, level I]

In terms of adverse events, there was no significant difference between acupuncture and wait-list control or sham acupuncture control. However, acupuncture had less adverse event compared with tricyclic antidepressants.[122, level I]

iii. Omega-3

In a Cochrane systematic review of 26 trials, there was small to modest benefit of omega-3 compared with placebo in mild to severe MDD (SMD= -0.30, 95% CI -0.10 to -0.50) but this effect was unlikely to be clinically meaningful. There was no significant difference between omega-3 and antidepressants in moderate to severe MDD.[123, level I]

iv. Folate

A Cochrane systematic review of three trials showed folate was more effective than placebo in MDD (WMD= -2.65, 95% CI -4.93 to -0.38). However, there was bias in the folate level of the participants and variation of dosage prescribed in the study.[124, level I]

> • There is insufficient evidence on the effectiveness and safety of acupuncture, omega-3 and folate in MDD.

v. Other Treatments
• Yoga

Yoga is a physical activity that involves mind-body medical intervention focusing on interactions of the brain, body, mind and behaviour.[125, level I]

A meta-analysis of nine RCTs of moderate quality found that yoga reduced symptoms of mild to moderate depression over usual care (SMD= -0.69, 95% CI -0.99 to -0.39), relaxation (SMD= -0.69, 95% CI -1.03 to -0.22) and aerobic exercise (SMD= -0.59, 95% CI -0.99 to -0.18) in 12 weeks only.[125, level I]

• Music Therapy

Music therapy, an intervention that involves regular meetings with a qualified music therapist, may help in modulating and improving mood through emotional expression.

A Cochrane systematic review of nine RCTs assessing music therapy in MDD showed that music therapy added to TAU was more effective than TAU alone in:[126, level I]
- clinician-rated depressive symptoms (SMD= -0.98, 95% CI -1.69 to -0.27)
- patient-reported depressive symptoms (SMD= -0.85, 95% CI -1.37 to -0.34)

• Dance Therapy

Dance Movement Therapy (DMT) uses bodily movement for exploration and expression of emotions. It can be done in groups or individually.

A Cochrane systematic review with low quality small studies showed no reliable effect of DMT on MDD. At the time of writing, DMT cannot be concluded to be effective for the treatment of MDD.[127, level I]

- **Hypnosis**

Hypnosis is a healing technique using the verbal hypnotic to bring the conscious mind to rest and the subconscious mind active to be receptive for positive suggestion to achieve a desired outcome.

There is no retrievable evidence on hypnosis in the treatment of MDD. A meta-analysis of six studies involving heterogeneous population (cancer patients, first time mothers and undergraduate students with depressive symptoms but unclear levels of severity) suggested that hypnosis can improve depressive symptoms (ES=0.57, 95% CI 0.319 to 0.813).[128, level I] However, the quality of the included studies was poor.

7.   COLLABORATIVE CARE MODEL

Collaborative care model is an integrated treatment approach between different health care providers working together with patients in a primary care setting aimed at achieving MDD recovery. The collaborative care involved enhanced collaborations among physicians, mental health specialists and care managers paired with depression-specific treatment guidelines, patients education and scheduled patient follow-up.[129 - 130, level I]

In a systematic review of 79 RCTs of adults with MDD, collaborative care was significantly more effective than usual care in improving depressive outcomes in acute phase of treatment (RR=1.32, 95% CI 1.22 to 1.43) and up to two years (RR=1.29, 95% CI 1.18 to 1.41). It also increased rates of antidepressant use up to 24 months (RR=1.22, 95% CI 1.03 to 1.45). This approach also showed improvement in mental health quality of life and patient satisfaction but not in physical health quality of life.[129, level I]

In an RCT of 581 patients with MDD, collaborative care improved depressive symptoms in acute (NNT=8) and continuation phase (NNT=6) compared with usual care.[131, level I]

NICE guidelines recommend collaborative care for moderate to severe depression in patients with CMI.[20]

A good quality RCT on patients with MDD and CMI showed that collaborative care were four times more likely to show response to treatment at six months compared with usual care (OR=4.04, 95% CI 2.01 to 8.31). The collaborative care involved enhanced collaborations among physicians, mental health specialists and care managers paired with depression-specific treatment guidelines, patients education and follow-up.[130, level I]

Recommendation 16
- Collaborative care may be considered in the acute and continuation phase treatment of major depressive disorder.

8. SPECIAL POPULATION

8.1 Major Depressive Disorder in Pregnant and Postpartum Women

Depression is the most highly prevalent mental health problem in perinatal population. Around 1 in 10 women suffer from perinatal depression worldwide as shown in a recent meta-analysis.[132, level III]

In Malaysia, using self-report measures by validated Malay version of Edinburgh Postnatal Depression Scale (EPDS) in health clinics, the prevalence of:
- antenatal depression ranges from 10.3% to 13.8%[133 - 134, level III]
- postnatal depression ranges from 3.9% to 21.08%[135 - 138, level III]

In hospital setting, the prevalence of postnatal depressions is:
- 6.8% in postnatal clinic using diagnostic assessment (MINI)[139, level III]
- 31.7% in postnatal ward using self-report (EPDS)[140, level III]

The national prevalence for postnatal depression from two large nation-wide surveys using EPDS ranges from 4.4% in health clinics[141, level III] to 12.7% in community setting.[142, level III]

Treating perinatal depression is essential in reducing symptomatology and preventing detrimental complications to women, children and the family. The most devastating consequences of perinatal depression and other mental disorders are a higher risk of suicidal ideation, suicidal attempt or suicide.[143, level III] In many developed countries, suicide is now one of the leading causes of maternal mortality; while the incidence of maternal death due to medical and obstetric factors are all decreasing.[144 - 145, level III]

Untreated depression in pregnancy is associated with an increased risk to the offsprings':
- fetal hyperactivity and irregular fetal heart rate[146, level III]
- premature delivery[146, level III]
- low birth weight[146, level III]
- increased rates of premature deaths and increased neonatal intensive care unit admission[147, level II-2]

Postnatal depression may impair the mother-infant relationship, which can lead to poor infant development and outcomes.[148, level II-2] Perinatal depression can also lead to difficult temperament, attentional, emotional and behavioral problems in children and adolescence.[149, level III]

In a naturalistic study of pregnant women with MDD, those who discontinued their medication showed significant increased risk of relapse (68%) compared with those continuing medication (26%).[150, level III]

8.1.1   Clinical Presentation

According to DSM-5, perinatal depression is MDD with peripartum onset i.e. when symptoms onset occurs during pregnancy or in the four weeks following delivery.[2] In clinical practice and in many research studies, however, postpartum period is defined up to one year, and self-report measures are used to identify perinatal depression.[151]

There is overlapping between MDD symptoms and normal pregnancy/postpartum e.g. fatigue, sleep disturbances and appetite changes. In a review on Asian population, some mothers tend to somatise and present with physical symptoms e.g. pain, body ache or headache rather than emotional symptoms.[152, level III]

A systematic review showed that risk factors for perinatal depression were:[153, level III]
- socioeconomic disadvantage (OR range=2.1 to 13.2)
- unintended pregnancy (OR range=1.6 to 8.8)
- younger age (OR range=2.1 to 5.4)
- unmarried (OR range=3.4 to 5.8)
- lack of intimate partner empathy and support (OR range=2.0 to 9.4)
- hostile in-laws (OR range=2.1 to 4.4)
- intimate partner violence (OR range=2.11 to 6.75)
- insufficient emotional and practical support (OR range=2.8 to 6.1)
- history of mental health problems (OR range=5.1 to 5.6)

Protective factors were:
- longer education (RR=0.5, p=0.03)
- being of the ethnic majority (OR=0.2, 95% CI 0.1 to 0.8)
- having a kind, trustworthy intimate partner (OR=0.52, 95% CI 0.30 to 0.90)

In a local nationwide study of 5,727 postnatal women, the risks for postnatal depression were:[141, level III]
- intimate partner violence (OR=2.34, 95% CI 1.12 to 4.87)
- emotional violence (OR=3.79, 95% CI 1.93 to 7.45)
- unplanned pregnancy (OR=3.32, 95% CI 2.35 to 4.69)
- lack of family support during confinement (OR=1.79, 95% CI 1.12 to 2.87)
- partner's use of alcohol (OR=1.59, 95% CI 1.07 to 2.35)
- low income household (OR=2.99, 95% CI 1.63 to 5.49)

8.1.2   Screening

Depression among perinatal women are not readily recognised and mostly underdiagnosed due to multiple help-seeking barriers.[154, level III] A systematic review of six RCTs showed that screening programmes for perinatal women with or without additional treatment components reduced risk of depression at 3 - 5 months follow-up by 18% to 59%

compared with no screening. The most widely used screening tool was EPDS. At the cut-off 13 of the English-version, its sensitivity and specificity ranged from 0.67 to 1.00 and 0.87 to 0.99 respectively.[155, level III]

Brief screening tools e.g. PHQ-2 and Whooley Questions may be useful in a two-stage screening. Whooley is 2-questions interview requiring health professionals to be trained to ask question sensitively. PHQ-2 is a self-report screening with Likert-response format. The sensitivity and specificity of PHQ-2 in perinatal women are 0.62 to 0.77 and 0.59 to 0.88 respectively.[155, level III] The sensitivity and specificity of Whooley questionnaire in antenatal women are 0.23 and 0.94 respectively,[156, level III] while the same measurements in postpartum are 1.00 and 0.44 respectively. [157, level III] In a 2-stage screening, PHQ-2 may be used followed by EPDS.

The suggested time-frame for EPDS screening is shown below:

Table 2. Time-frame for EPDS screening

Period	First Screening	Repeat
Antenatal	Within four weeks of booking or as early as practical in pregnancy	• At least once in third trimester of pregnancy • At any time in pregnancy if clinically indicated
Postnatal	6 - 12 weeks after birth	• At least once in the first postnatal year • At any time in the first postnatal year if clinically indicated

Adapted: Austin M-P, Highet N and the Expert Working Group (2017) Mental Health Care in the Perinatal Period: Australian Clinical Practice Guideline. Melbourne: Centre of Perinatal Excellence; 2017

NICE recommends to consider asking Whooley Questions at a woman's first contact at primary care or her booking visit, and during the early postnatal period. If she responds positively to either questions or there is clinical concern, consider using EPDS or PHQ-9 or refer to her GP or mental health professional according to severity.[158]

Malay language PHQ-2 has been validated as part of PHQ-9.While Malay-language EPDS has been validated with a sensitivity of 0.727 and specificity of 0.92 at the cut-off 12.[136, level III] The CPG DG opines that a two-stage screening is appropriate in perinatal women in local context. Refer to **Appendix 6B** and **7** for **Malay version of PHQ-2** and **EPDS**.

> **Recommendation 17**
> • Screening for perinatal depression may be done in a two-stage approach.
>   ○ Use brief screening tools e.g. Patient Health Questionnaire-2 or Whooley Questions in the first stage.
>   ○ If there is positive response to the brief screening tools, Edinburgh Postnatal Depression Scale should be used for further screening.

8.1.3 Diagnosis

Diagnosis of perinatal depression is made using DSM-5 Criteria for MDD, with peripartum onset, and can be categorised to mild, moderate or severe.[2]

8.1.4 Assessment

Besides assessing clinical symptoms, psychosocial risks and risk of suicide (refer to **Subchapter 2.4**), other assessment that should be done in perinatal women are risk of infanticide and mother-infant interaction.[159]

8.1.5 Treatment

The principles of treatment for perinatal depression must be based on risk-benefit analysis and shared decision making. The clinician should discuss potential harms and benefits of antidepressants with the patient so that she can make well-informed decisions on preferred treatment.[160]

> • Clinicians must discuss with the women and, where possible, their significant other(s) on the following:[158, 159]
>   ○ benefits and potential risks of treatment to mother and foetus/ breastfed baby in both short- and long-term; and possible consequences of no treatment or if treatment is changed or stopped abruptly
>   ○ uncertainty of benefits and risks in perinatal period
>   ○ patient's preference
> • Increased level of maternal and foetal/baby monitoring and support is crucial in perinatal period.

Pre-pregnancy Care

Women in their reproductive age with mental health problems (including MDD) should receive pre-pregnancy care (PPC) in a nearby health clinic or an obstetric and gynaecology clinic in a hospital, at least three months prior to conception.[161, level III]

PPC is the provision of biomedical, behavioural and social health interventions to women and couples before conception occurs, aimed

at improving their health status, and reducing behaviours and individual and environmental factors that could contribute to poor maternal and child health outcomes.[162, level III]

In PPC, treatment of pre-existing MDD must be optimised and contraception may be provided. Ideally, whenever possible, the aim of optimisation of treatment is to achieve remission of MDD with completion of maintenance and continuance therapy. Otherwise, risks and benefits of continuing antidepressant treatment and consequences of stopping abruptly or changing treatment must be discussed, taking into consideration the severity of MDD and risk of relapse or recurrence.

A.   Pharmacotherapy
i.   Efficacy
In general, antidepressants are effective for perinatal depression based on extrapolation of evidence on general adults.[20] SSRIs are more effective than placebo at 4 - 8 weeks for postpartum depression:[163, level I]
  • RR for response=1.43 (95% CI 1.01 to 2.03)
  • RR for remission=1.79 (95%CI 1.08 to 2.98)

ii.   Safety Profile in Pregnancy
Second-generation antidepressants including SSRI for depression in pregnancy may be associated with increased risk of some serious harms although the absolute risks of harm appear to be small. [155, level III; 158; 159]

SSRIs are the most well-studied antidepressant compared to other antidepressants. When counselling the benefit and risks of treatment, use absolute risk values based on a common denominator (i.e. numbers out of 100 or 1000) than RR values to reflect risks more accurately to the woman.[158] Increase in absolute risks of adverse outcome associated with medications during pregnancy compared with pregnancy without medications are as below (refer to **Table 3**).[159]

Table 3. Absolute risks of adverse outcome associated with medications during pregnancy

Medications	Outcome	Absolute risk in pregnant women not taking medications per 1000	Absolute risk in pregnant women taking medications per 1000	Absolute risk difference per 1000	Possible association (Absolute risk difference per 1000)
Any antidepressant	Poor neonatal adaptation syndromes[2]	86	366	280	Paroxetine (107)
	Respiratory distress[2]	36	128	90	
	Tremors[2]	92	444	352	
SSRI	Cardiac malformation[2]	34	46	12	Citalopram (35) Escitalopram (4) Fluoxetine (7) Paroxetine (7)
	Cardiac malformation[2]	11	13	2	Citalopram (2) Escitalopram(10) Fluoxetine (4) Paroxetine (3)
	Miscarriages[1]	81	109	28	
	Premature birth[1]	60	161	99	
	Neonatal convulsions[1]	3	4 - 15	1 - 12	
	Persistent pulmonary hypertension[1]	3	4	1	
	Respiratory distress[1]	32	45	13	
SNRI	Miscarriages[1]	81	138	57	
TCA	Miscarriages[1]	81	107	26	
	Premature birth[2]	53	100	47	
Long-acting Benzodiazepines (repeated prescription around the time of birth)	Respiratory distress[1]	32	72	40	

Adapted:
1. Austin M-P, Highet N and the Expert Working Group (2017) Mental Health Care in the Perinatal Period: Australian Clinical Practice Guideline. Melbourne: Centre of Perinatal Excellence; 2017
2. National Collaborating Centre for Mental Health. Antenatal and postnatal mental health Clinical management and service guidance. United Kingdom: The British Psychological Society and The Royal Collage of Psychiatrists; 2014

In a cohort study, there was no significant difference in major birth defects between mirtazapine and SSRIs. In another analysis, there was a higher rate of birth defects in mirtazapine compared with general control after exclusion of chromosomal or genetic anomalies (OR=3.3, 95% CI 1.04 to 10.3). However, if first trimester exposure were excluded, the difference was not significant.[76, level II-2]

A systematic review showed that antidepressants were associated with maternal adverse outcomes in pregnancy:[155, level III]
- preeclampsia
  - venlafaxine (RR=1.57, 95% CI 1.29 to 1.91)
- vaginal bleeding during pregnancy or postpartum hemorrhage
  - SSRI + venlafaxine (RR=1.46, 95% CI 1.29 to 1.65)

There is lack of strong evidence indicating detrimental effects of antidepressants on low birth weight and, neurodevelopmental and neurobehavioural outcomes.[164, level II-2]

- Extreme caution is needed in interpreting the data on antidepressant in pregnancy due to the small absolute risks in most cases and the uncertainty of whether effects due to the medications, depression itself or other confounding factors.[158]

Refer to **Appendix 8** on **FDA Pregnancy Categories**.

iii.   Safety Profile in Breastfeeding
In general, a relative infant dose (RID) below 10% of the average maternal level of an antidepressant is considered safe.[165, level III]

A systematic review on SSRIs and SNRIs which largely represented by case reports and small studies found the following medications with their range of RID:[166, level I]
- escitalopram: 4.50 - 6.40%
- fluoxetine: 2.40 - 6.80%
- fluvoxamine: 0.20 - 0.62%
- paroxetine: 0.30 - 2.9%
- sertraline: 0.50 - 3.70%
- duloxetine: 0.14 - 0.82%
- venlafaxine: 3.20 - 8.10%

In another review, safety of mirtazapine during lactation was inconclusive.[167, level III]

The effects of antidepressants on breastfed babies were occasional, mild-moderate and short-term with inadequate data on long term effects. Sertraline and paroxetine had better neonatal safety profile during breastfeeding compared with other SSRIs/SNRIs.[166, level I] Both systematic reviews did not report on quality assessment.

> • Breastfeeding is encouraged regardless of types of antidepressant taken by mothers with infant monitoring of adverse effects e.g. over-sedation.[160]

B.   Psychosocial Intervention and Psychotherapy

Four meta-analyses showed that psychosocial interventions (e.g. peer support and non-directive counseling) and psychotherapy (e.g. IPT, CBT and psychodynamic therapy) were significantly effective in reducing depressive symptoms compared to control in perinatal depression. [168 - 171, level I]

Other interventions that have shown some benefits in perinatal depression include mindfulness-based intervention and web-based intervention.[172 - 173, level I]

A Cochrane systematic review showed that psychosocial or psychological interventions (i.e. intensive, individualised postpartum home visits provided by public health nurses or midwives; lay (peer)-based telephone support and IPT) significantly prevented postpartum depression compared with standard care.[174, level I]

Besides treating mother's depression, treatment must also aim to prevent or reduce the effects of postpartum depression on the children. Women with depression and mother-infant interaction difficulties may benefit from individual mother–infant interventions that will improve mother–infant attachment problems and mother-infant behaviour management problems.[158, 159]

C.   Electroconvulsive Therapy

NICE guidelines recommend considering ECT for pregnant women with severe depression, severe mixed affective states or mania, or catatonia, whose physical health or that of the foetus is at serious risk.[158]

COPE guidelines recommend considering ECT when a postnatal woman with severe depression:[159]
- has not responded to one or more trials of antidepressants of adequate dose and duration or where there is a high risk of suicide or high level of distress
- when food or fluid intake is poor
- in the presence of psychotic or melancholic symptoms

D.   Other Therapy

Evidence is too inconclusive for depression-specific acupuncture, maternal massage, bright light therapy and omega-3 fatty acids for antenatal depression.[174, level I]

E.   Choice of Treatment

Given the uncertainty on risk-benefit ratio of antidepressants in perinatal women, the threshold for pharmacotherapy intervention should be higher while psychological interventions should always be strongly considered.

i.   Mild-moderate

Most guidelines recommend on psychotherapy as the initial treatment for mild to moderate perinatal depression.[160]

ii. Severe

Most guidelines recommend pharmacotherapy intervention as the initial treatment for severe perinatal depression.[160]

- Prescribing medications in perinatal women is complex and there are preference to non-pharmacological intervention among this population.[154, level III]
- Most guidelines acknowledge the importance of individually-tailored medicine in perinatal depression. Decision-making process should take into consideration:[160]
  - psychiatric history and indication for antidepressant medication
  - current psychiatric symptoms
  - previous attempts of tapering medication
  - availability of alternative treatment options such as psychotherapy and the presence of a social support

Recommendation 18
- For mild to moderate perinatal depression, psychotherapy, e.g. interpersonal psychotherapy and cognitive behavioural therapy, should be considered as initial treatment.
- Psychosocial interventions i.e. peer support and non-directive counseling may be considered in mild to moderate postpartum depression.
- For severe perinatal depression, pharmacotherapy intervention should be considered and selective serotonin reuptake inhibitors are the preferred choice. Once medications have become effective, psychotherapy may be recommended as an adjunct.

8.2   Major Depressive Disorder in the Elderly

It is estimated that the proportion of the world's population of elderly aged over 60 years old will increase from 12% in 2015 to 22% in 2050. Unipolar depression in elderly occurs in 7% of the general elderly population and accounts for 5.7% of YLD.[213]

A meta-analysis of 74 studies showed a median prevalence rate of depression in the elderly at at 10.3% (IQR of 4.7% - 16.0%).[175, level III] Local studies showed different prevalence of depression according to setting; 20.9% among Malay elderly in Klang Valley,[176, level III] and 30.1% among Malay elderly residing in rural area.[177, level III]

8.2.1   Clinical Presentation and Diagnosis

Depression in elderly population can present in many ways; either as a new onset depression, recurrent MDD that started earlier in life, a mood disorder that is related to other medical problems or mood symptoms related to substance or medication use.[178, level III]

MDD in elderly can be diagnosed based on ICD or DSM criteria. However, some diagnostic criteria may overlap with symptoms of major neurocognitive disorder or physical illness especially neurological disorder in the elderly.[179, level III] A meta-analysis of 11 observational studies showed that depressed elderly presented with more agitation (OR=1.84, 95% CI 1.39 to 4.45), general somatic symptoms (OR=2.01, 95% CI 1.38 to 2.92), GI somatic symptoms (OR=1.58, 95% CI 1.27 to 1.97) and hypochondriasis (OR=3.13, 95% CI 2.24 to 4.38) than younger adults with depression.[180, level III]

The following symptoms may suggest MDD in elderly:[21]
- psychomotor retardation
- poor concentration
- constipation
- poor perceived health
- prominent anxiety symptoms
- cognitive deficits
- prominent somatic symptoms

In a cohort study among elderly (mean age of 70.6 years) in Netherlands, depressed elderly had significantly lower education level, divorced or widowed and lower Mini Mental State Examination (MMSE) score compared with those who were non-depressed. Only 33.1% of the patients were in their first episode of depressive disorder and 41% had co-morbid anxiety disorder over the past six months.[181, level II-2]

Depression in elderly population was also associated with higher morbidity and mortality. In a population-based cohort study, high levels of depressive symptoms (≥16 on 20-item Center for Epidemiologic Studies Depression Scale) was significantly associated with increased risk of developing coronary heart disease, stroke and combination of both diseases.[182, level III] A cohort study of elderly men aged ≥75 years in Australia showed a HR for mortality of 1.66 (95% CI 1.08 to 2.56) for depressed elderly men compared with non-depressed elderly men at baseline.[183, level II-2]

8.2.2   Assessment

Assessment of MDD in elderly population is similar to the assessment in general adults. Organic causes of depression need to be ruled out and appropriate laboratory investigations to be done when necessary. Refer to **Appendix 5**.

8.2.3   Screening

A systematic review of 133 studies involving 46651 participants identified 16 screening instruments for depression in elderly population. Majority of the studies used self-rating scales; the most common were various versions of Geriatric Depression Scale (GDS). The pooled sensitivity and specificity are shown in **Table 4**.[212, level III]

Table 4. Sensitivity and specificity of self-rating scale instruments

Instrument	Sensitivity	Specificity
GDS-30	82.8% (95% CI 80.7 to 87.4)	72.2% (95% CI 63.1 to 80.8)
GDS-15	84.4% (95% CI 80.5 to 87.4)	77.4% (95% CI 72.1 to 82.0)
Whooley Questions	91.8% (95% CI 85.2 to 95.6)	67.7% (95% CI 58.1 to 76.0)

- Awareness needs to be created at community and primary health care level to screen for and identify depression, particularly in those identified as high risk given the higher morbidity and mortality among the depressed elderly.
- There is no evidence on targeted screening among the elderly. However, healthcare providers may screen them for depression if they present with the symptoms mentioned above. Both GDS[184, level III] and Whooley Questions has been validated locally.

8.2.4   Treatment

A. Psychotherapy

A Cochrane systematic review found that IPT combined with antidepressant reduced recurrence of MDD in elderly at 12 months compared with placebo (RR= 0.42, 95% CI 0.23 to 0.77). No significant difference in overall drop-out rate was noted between the two groups.[188, level I]

Another systematic review showed that PST reduced depressive symptoms in older adults with MDD compared to control conditions Cohen's d=1.15 (p=0.00006). There were no significant differences in drop-out rates between PST and control.[191, level I]

In the latest systematic review that focused on non-pharmacotherapy treatment for depressed elderly in primary care, CBT reduced depressive symptoms compared with control condition at long-term follow-up but the effect size was small (SMD= -0.21, 95% CI -0.40 to -0.03).[192, level I]

The primary papers used in the three meta-analyses were of moderate quality.

Recommendation 19
- Psychotherapy should be offered for major depressive disorder in the elderly.

B. Pharmacotherapy

There are four meta-analyses with moderate risk of bias of primary papers and one RCT on the effectiveness of antidepressants in treating depression in elderly population.

In a Cochrane systematic review on depression in elderly, TCAs, SSRIs (fluoxetine) and MAOIs were significantly more effective in preventing persistence of symptoms compared with placebo with NNT of 3.97 (95% CI 3.88 to 4.05), 8.45 (95% CI 8.38 to 8.53) and 3.14 (95% CI 2.99 to 3.29) respectively.[185, level I] However, in a recent meta-analysis using different RCTs on several SSRIs (fluoxetine, escitalopram, citalopram) in depressed elderly, there was no significant difference in effectiveness between the SSRIs and placebo in both response and remission. On the other hand, duloxetine was more effective than placebo in response (OR=2.83, 95% CI 1.96 to 4.08) and remission (OR=1.78, 95% CI 1.20 to 2.65).[186, level I]

In another Cochrane review, there was no difference in effectiveness between TCAs and SSRIs, MAOIs and 'atypical antidepressants' (buspirone, buproprion, milnacipran, venlafaxine, reboxetine and mirtazapine) on depression in elderly.[187, level I]

A recent Cochrane systematic review on three RCTs showed that antidepressants (SSRIs and TCAs) in continuation and maintenance phase in elderly with MDD reduced recurrence at 12 months compared with placebo (RR=0.67, 95% CI 0.55 to 0.82; NNTB=5). However, the trials included were of low quality with marked heterogeneity among them.[188, level I]

An RCT showed no significant difference between sertraline and nortriptyline in response and remission rates of older adults with melancholia or non-melancholia depression.[189, level I]

SSRIs were less likely to cause withdrawal due to side effects compared with TCAs (RR=1.36, 95% CI 1.09 to 1.70) in elderly with depression. There was no significant difference in other comparison i.e. between TCAs and MAOIs or 'atypical antidepressants'.[187, level I]

Citalopram had larger proportion of adverse events (fatigue, sweating and tremors) compared with placebo in depressed elderly. There was

no significant difference in frequency of AEs between other SSRIs in similar comparison. On the other hand, duloxetine was significantly associated with increased risk of dry mouth, constipation, diarrhoea and dizziness compared with placebo.[186, level I]

A cohort study of 60,746 elderly patients diagnosed with MDD showed that SSRIs were associated with the highest risk for falls (HR=1.66, 95% CI 1.58 to 1.73) and hyponatraemia (HR=1.52, 95% CI 1.33 to 1.75) compared with when the antidepressants were not being used. While other antidepressants group (duloxetine, flupentixol, L-tryptophan, mirtazepine, nefazodone, reboxetine, tryptophan and venlafaxine) was associated with the highest risks for all-cause mortality (HR=1.66, 95% CI 1.56 to 1.77), attempted suicide/self-harm (HR=5.16, 95% CI 3.90 to 6.83), stroke/transient ischaemic attack (HR=1.37, 95% CI 1.22 to 1.55), fracture (HR=1.63, 95% CI 1.45 to 1.83) and epilepsy/seizures (HR=2.24, 95% CI 1.60 to 3.15) in similar comparison.[190, level II-2]

Recommendation 20
• Antidepressants should be considered with caution on tolerability issues for major depressive disorder in the elderly.

C. Electroconvulsive Therapy

An updated Cochrane systematic review found that unilateral and bilateral ECT (six treatments) reduced depressive symptoms measured with MADRS compared with simulated group in depressed elderly (p<0.05). There was no significant difference between unilateral and bilateral ECT in reduction of depression symptoms after five treatments or three weeks of treatment. Three-times weekly ECT was shown to have lower depressive symptoms compared with once-weekly ECT at week 4 (p<0.001). In one of the included RCT, in terms of cognitive side effects, bilateral ECT had significantly lower mean MMSE scores after 8, 12 and 16 ECT sessions compared with right unilateral ECT.[193, level I]

A systematic review of maintenance ECT with nortriptyline for MDD with psychosis in elderly showed that mean survival time to relapse or recurrence was longer (23 months) compared with continuing nortriptyline only (16 months) with HR=8.12 (95% CI 1.5 to 44.7). However, there was no quality assessment of the RCTs.[194, level I]

The elderly with MDD have an increased likelihood of having co-morbid medical illness thus consultation with other specialty is recommended during pre ECT assessment. Patients with co-morbid dementia are at risk of developing post-ECT delirium and should be monitored closely.[195]

> **Recommendation 21**
> • Electroconvulsive therapy may be offered in elderly with major depressive disorder after assessment of possible co-morbidities.

D. Exercise Therapy

In a systematic review on depressed elderly patients, exercise as an adjunct to antidepressants showed some effectiveness in reducing depressive symptoms compared with control.[196, level I]

Another systematic review of eight RCTs on elderly participants with depressive symptoms supported the finding when it showed that exercise improved depressive symptoms compared with controlled conditions (SMD=0.90, 95% CI 0.28 to 1.51). All studies were considered to be of low quality with significant heterogeneity.[197, level I]

8.2.5   Treatment-resistant Depression

There are limited RCTs on the management of TRD among elderly population.

In a small RCT on elderly with TRD, venlafaxine was more effective than paroxetine on CGI (p<0.000002) and HAM-D measures (p<0.0003).[198, level I] In another RCT, the use of aripiprazole as augmentation to venlafaxine in the same population had higher percentage of remission compared with placebo (OR=2.0, 95% CI 1.1 to 3.7).[199, level I]

8.3   Major Depressive Disorder in Patients with Chronic Medical Illness

Presence of chronic medical illness (CMI) together with depression are common and has bidirectional relationship. This CPG addresses common CMI i.e. diabetes mellitus, coronary heart disease, cancer, end-stage kidney disease and post-stroke in MDD. Adverse health risk behaviours and psychobiological changes in depression increases the risk of CMI while biological changes and complications of CMI may precipitate depression.[200, level III]

A meta-analysis of 83 cross-sectional studies of outpatients having CMI from different clinical specialties found overall pooled prevalence of depression or depressive symptoms at 27.0% (95% CI 24.0 to 29.0). There was a higher prevalence of depression or depressive symptoms in outpatients with CMI with an OR of 3.16 (95% CI 2.66 to 3.76) compared with healthy controls.[201, level III]

A population-based study found that acute life stress, number of CMI and family support satisfaction were the three strongest predictors of depressive symptoms in CMI.[202, level III]

8.3.1   Screening

For CMI-associated functional impairment, NICE guidelines recommend the use of Whooley 2-Questions to screen for depression.[216]
Following 'Yes' to either question, proceed with these:[216]
- During the last month, have you often been bothered by feelings of worthlessness?
- During the last month, have you often been bothered by poor concentration?
- During the last month, have you often been bothered by thoughts of death?

8.3.2   Assessment

In addition to assessment of depression in **Subchapter 2.3**, include following assessment for patients with CMI:[216]
- a. role of CMI and any prescribed medication in the development or maintenance of depression
- b. provision and compliance to optimal treatment for CMI, with proper referral to other specialities if there are issues

8.3.3   Diagnosis and Classification

There is overlapping of somatic symptoms in depression and CMI e.g. fatigue, changes in appetite, psychomotor disturbances and sleep disturbances.

In a community-based study on MDD, the agreement of five non-somatic DSM IV criteria (low mood, loss of interest or pleasure, guilt/ worthlessness, impaired concentration/indecisiveness and suicidal ideation) and full DSM IV criteria for MDD was 93.7%.[203, level III] Therefore, in diagnosing MDD in patients with CMI, emphasis must be given to the non-somatic criteria.

In managing MDD in chronic medically ill patients, it will be useful to classify cases based on severity of symptoms. NICE guidelines classify depression in patients with CMI into the following:[216]
- subthreshold depressive symptoms: fewer than five symptoms of depression
- mild depression: few, if any, in excess of the five required to make the diagnosis of MDD, and the symptoms result in only minor functional impairment
- moderate depression: symptoms or functional impairment between mild and severe
- severe depression: most symptoms, and the symptoms markedly interfere with functioning; can occur with or without psychotic symptoms

For the purpose of this CPG, evidence on mild to severe MDD with CMI is addressed.

8.3.4 Treatment
A. Psychosocial Interventions and Psychotherapy

Generally, psychosocial interventions and psychotherapy for MDD in patients with CMI are based on severity of depression as recommended in **Chapter 4**. In addition, NICE guidelines also recommend a structured group physical activity and a group-based peer support (self-help) programme for mild to moderate depression in CMI.[216]

i. Depression with Diabetes Mellitus

A Cochrane systematic review of eight RCTs on patients diagnosed with diabetes mellitus (DM) found that psychotherapy comprised with CBT, web-based CBT, telephone CBT plus walking programme, minimal psychological intervention and psychodynamic supportive therapy was beneficial in depression remission both at short-term (OR=2.88, 95% CI 1.58 to 5.25) and medium-term follow-up (OR=2.49, 95% CI 1.44 to 4.32).[204, level I]

In another systematic review that involved 31 RCTs, psychosocial interventions were effective in reducing depressive symptoms (SMD= -1.50, 95% CI -1.83 to -1.18) in acute treatment phase of depression in patients diagnosed with type 2 DM.[205, level I]

Both SR included moderate quality papers.

ii. Depression with Coronary Heart Disease

A systematic review by Cochrane of 19 RCTs showed that psychosocial interventions and psychotherapy (group and individual-based therapy based on CBT components, counselling, stress reduction, telephone-based counselling, home-based intervention, telephone-based CBT and transcendental meditation technique) either alone or with other cardiac rehabilitation reduced depressive symptoms compared with usual care or other types of rehabilitation (SMD= -0.27 95% CI -0.39 to -0.15).[206, level I]

Another Cochrane review revealed that CBT improved depression score at short-term with SMD of -0.81 (95% CI -1.26 to -0.36) and long-term with SMD of -0.75 (95% CI -1.20 to -0.30).[207, level I]

The primary papers included in both reviews were of moderate quality.

B. Pharmacotherapy

When an antidepressant is prescribed for a patient with depression and underlying CMI, the following must be taken into consideration:[216]
- presence of additional medical problems
- side effects of antidepressants, which may affect the underlying medical illness (in particular, SSRIs may result in or exacerbate hyponatraemia, especially in older patients)
- interactions with other medications prescribed for underlying CMI

i.   Depression with Diabetes Mellitus

In a Cochrane SR that included eight RCTs on depression and DM, when compared with placebo:[204, level I]

- ○ antidepressants reduced depressive score at short-term (SMD= -0.61, 95% CI -0.94 to -0.27)
- ○ antidepressants had beneficial effect in depression remission at short-term (OR=2.50, 95% CI 1.21 to 5.15)
- ○ SSRIs (sertraline, paroxetine and fluoxetine) showed improvement in glycaemic control at short-term with MD for HbA1c of -0.4% (95% CI -0.6 to -0.1)

Studies included were mostly of moderate quality with low heterogeneity.

ii.   Depression with Coronary Heart Disease

A Cochrane systematic review of eight trials showed that SSRIs (sertraline, fluoxetine or citalopram) reduced short-term depression score (SMD= -0.24, 95% CI -0.38 to -0.09) compared with placebo in depression with coronary artery disease. There was no significant difference in recurrent non-fatal myocardial infarction, congestive heart failure, recurrent angina pectoris or reduction of cardiac procedures in similar comparison.[207, level I]

iii. Depression with Cancer

A Cochrane systematic review of nine RCTs found no significant difference in effectiveness between antidepressant (fluoxetine and mianserin) and placebo at 6 to 12 weeks in patients with cancer. There was also no significant difference between SSRIs (paroxetine or fluoxetine) and TCAs (amitriptyline or desipramine) in similar outcome and in dropouts due to ineffectiveness and side effects.[208, level I]

In a meta-analysis of eight RCTs, antidepressant reduced depressive symptoms in cancer patients with MDD compared with placebo (SMD= -0.596, 95% CI -1.041 to -0.150).[209, level I]

iv. Depression with End-stage Renal Disease

An updated Cochrane SR on depression with end-stage kidney disease treated with dialysis found that when compared with placebo:[210, level I]

- ○ sertraline reduced depressive symptoms (MD for BDI score= -7.50, 95% CI -11.94 to -3.06)
- ○ escitalopram reduced depressive symptoms (p=0.001)
- ○ SSRIs (fluoxetine, sertraline and escitalopram) increased nausea (RR=2.67, 95% CI 1.26 to 5.68)

There were no significant risk of antidepressant causing hypotension, headache, and sexual dysfunction compared with placebo. However, the four studies included in the review were of low quality.

v. Depression in Post-Stroke

An updated Cochrane SR found that antidepressants were more effective in achieving remission with OR of 0.47 (95% CI 0.22 to 0.98) compared with placebo in patients who developed depression after stroke.[211, level I]

The most common adverse events reported involved:[211, level I]
- ○ central nervous system e.g. confusion, sedation and tremors (OR=1.96, 95% CI 1.19 to 3.24)
- ○ GI system e.g. constipation and diarrhoea (OR=2.37, 95% CI 1.38 to 4.06)

The studies included in the review were of moderate quality.

Recommendation 22
- Screening for depression should be done in patients with chronic medical illness (CMI) with related functional impairment.
- Psychosocial intervention and psychotherapy should be considered in patients with major depressive disorder (MDD) and CMI.
- If pharmacotherapy is required for patients with MDD and CMI, consider antidepressants with the least drug-drug interactions.

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9. FOLLOW-UP AND MONITORING

Pre-treatment screening and monitoring of treatment in MDD are proposed in **Table 5**.

Table 5. Ongoing monitoring during treatment of MDD

Parameter	Agent	Frequency of the monitoring parameter	Comments
Body Mass Index and waist circumference	NASSAs MAOIs TCAs	Baseline and at 6-monthly	
Blood pressure	Venlafaxine TCAs MAOIs	At Baseline, with significant dose increase and 3 to 6-monthly after stabilisation	Closer monitoring of MAOIs in first weeks until tolerance occurs
Electro-cardiogramme for QT prolongation	TCAs	At baseline, after initial dose titration and at change of dose	In individuals over 45 years of age or with cardiovascular (CV) disorders
	SNRIs SSRIs	At baseline	In individuals with CV risk
Liver function test	Agomelatine	At baseline 3, 6, 12 and 24 weeks after initiation dosage, after dosage increment or when clinically indicated	Treatment should be discontinued if transaminases exceed three times upper limit of normal
Electrolytes	SSRIs Mirtazapine SNRIs TCAs	At baseline and one month after treatment initiation or if clinically indicated in high risk groups*	• More frequent monitoring in elderly or those with existing hyponatraemia • Need to monitor together with urine and serum osmolality since SSRIs can induced hypovolemic hyponatremia via Syndrome of Inappropriate Antidiuretic Hormone Secretion
Full blood count	Mirtazapine Mianserin	If clinically indicated	To detect blood dyscrasia (e.g. neutropenia and thrombocytopaenia)
Bone mineral density	SSRIs	If clinically indicated in high risk groups for osteoporosis**	Refer to Fracture Risk Assessment Tool Score in MoH CPG Management of Osteoporosis, 2012

*previous history of antidepressant-induced hyponatremia, advanced age, low body weight, thiazide and carbamazepine use
**based on Fracture Risk Assessment Tool Score

Adapted: Dodd S, Malhi GS, Tiller J, et al. A consensus statement for safety monitoring guidelines of treatments for major depressive disorder. Aust N Z J Psychiatry. 2011;45(9):712-725

10. IMPLEMENTING THE GUIDELINES

The management of MDD should be guided by evidence-based approach in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

10.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:
   a. wide dissemination of the CPG to healthcare providers (hard- and soft-copies)
   b. regular topic update for healthcare providers via continuous medical education (seminar/conference/course)
   c. involvement of governmental/NGOs e.g. World Mental Health Day, Suicide Prevention Day etc.
   d. accessibility to relevant multidisciplinary teams

Existing barriers for application are:
   a. low mental health literacy
   b. insufficient resources in terms of budget, expertise, medications, access to psychotherapy
   c. no national registry
   d. variation in clinical management and preferences
   e. low priority on the issue by the stakeholders

10.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:
   a. ensure widespread distribution of the CPG to health care personnel via printed copies, electronic websites, etc.
   b. reinforce training of health care personnel by regular seminars or workshops to ensure information is made available
   c. develop multidisciplinary teams at hospital and community level to include involvement of specialists, medical/dental officers, pharmacists, allied health professional and nurses

The following is proposed as a clinical audit indicator for quality management of MDD:

$$\text{Percentage of moderate to severe MDD prescribed with SSRIs/SNRIs/ NaSSA} = \frac{\text{Number of moderate to severe MDD prescribed with second-generation antidepressants in a period}}{\text{Number of moderate to severe MDD In the same period}} \times 100\%$$

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: What are the safe and effective treatments in MDD?

1. DEPRESSIVE DISORDER, MAJOR/
2. (major depress* adj1 disorder*).tw.
3. DEPRESSIVE DISORDER/
4. ((neuro* or endogenous or syndrome or disorder or unipolar or psycho*) adj1 depress*).tw.
5. melancholia*.tw.
6. 1 or 2 or 3 or 4 or 5
7. COGNITIVE THERAPY/
8. (cogniti* adj1 (therap* or psychotherap*)).tw.
9. behavio* therap*, cognitive.tw.
10. therap*, cognitive behavio*.tw.
11. computerised cognitive behavio* therap*.tw.
12. internet-based cognitive behavio* therap*.tw.
13. brief cognitive behavio* therap*.tw.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 6 and 14
16. limit 15 to (yr="2006 -Current" and "all adult (19 plus years)" and english and humans)

Appendix 2

CLINICAL QUESTIONS

1. What are the accurate screening tools in population at-risk of MDD?
2. What are the accurate diagnostic tools in MDD?
3. What are the safe and effective pharmacotherapy treatments in MDD?
   - Selective serotonin reuptake inhibitors (SSRIs)
   - Serotonin noradrenaline reuptake inhibitors (SNRIs)
   - Noradrenergic and specific serotonergic antidepressants (NaSSAs)
   - Monoamine oxidase inhibitors (MAOIs)
   - Tricyclic antidepressants (TCAs)
   - melatonergic agonist & serotonergic antagonist (agomelatine)
   - Multi-modal antidepressants
   - Psychostimulants
   - Benzodiazepines
   - Ketamine
4. What are the effective and safe optimisation/switching/augmentation/combination strategies of pharmacotherapy treatment in MDD?
5. What are the safe and effective non-pharmacotherapy treatments in MDD?
   - Psychological/Behavioural interventions
     - Cognitive behavioural therapy (CBT)
     - Interpersonal psychotherapy (IPT)
     - Problem-solving therapy (PST)
     - Behavioural therapy
     - Third-wave CBT
     - Psychodynamic psychotherapy
     - Marital therapy
     - Internet- and mobile/computer-based interventions
   - Psychosocial interventions
     - Psycho-education
     - Counselling
     - Non-directive supportive therapy
     - Exercise
     - Relaxation
     - Psychospiritual
   - Physical treatments
     - Electroconvulsive therapy (ECT)
     - Repetitive transcranial magnetic stimulation (rTMS)
6. What are the safe and effective traditional, complementary and alternative treatments in MDD?
7. What are the safe and effective treatments for treatment-resistant MDD?

8. How effective are collaborative care models in the management of MDD?
9. What are the safe and effective treatments in special populations with MDD?
   - Elderly
   - Pre- and post-natal women
   - Patients with co-morbid chronic medical illnesses
10. What are the criteria for referral and admission of patients with MDD?
11. What are the parameters to be monitored in patients with MDD on treatment?

Appendix 3

**AMERICAN PSYCHIATRIC ASSOCIATION'S
DIAGNOSTIC AND STATISTICAL MANUAL OF
MENTAL DISORDERS, FIFTH EDITION (DSM-5)
MAJOR DEPRESSIVE DISORDER**

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly attributable to another medical condition.
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note**: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note**: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A–C represent a major depressive episode.
Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability)

may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.
Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Source: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington: American Psychiatiric Association; 2013

Appendix 4

10th REVISION OF THE INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD-10)

Typical symptoms of depressive episodes
- Depressed mood
- Loss of interest and enjoyment
- Reduced energy

Common symptoms of depressive episodes
- Reduced concentration and attention
- Reduced self-esteem and self-confidence
- Ideas of guilt and unworthiness
- Bleak and pessimistic views of the future
- Ideas or acts of self-harm or suicide
- Disturbed sleep
- Diminished appetite

Mild depressive episode
- At least 2 typical symptoms plus 2 common symptoms
- No symptom should be present to an intense degree
- Minimum duration of whole episode is at least 2 weeks
- The person has some difficulty in continuing ordinary work and activities

Moderate depressive episode
- At least 2 typical symptoms plus 3 common symptoms
- Some symptoms may be present to a marked degree
- Minimum duration of whole episode is at least 2 weeks
- The person has considerable difficulty in continuing social, work or domestic activities

Severe depressive episode without psychotic symptoms
- All 3 typical symptoms plus at least 4 common symptoms
- Some of the symptoms are of severe intensity
- Minimum duration of whole episode is at least 2 weeks (may be <2 weeks if symptoms are very severe and of very rapid onset)
- The person is very unlikely to continue with social, work or domestic activities

Severe depressive episode with psychotic symptoms
- A severe depressive episode
- Delusions, hallucinations or depressive stupor are present

Recurrent depressive disorder
- Repeated depressive episodes (mild, moderate or severe)
- No history of independent manic episodes

Recurrent depressive disorder, current episode mild
- Fulfils criteria for recurrent depressive disorder
- Current episode fulfils criteria for mild depressive episode
- At least 2 episodes lasted a minimum of 2 weeks, and were separated by several months without significant mood disturbance

Recurrent depressive disorder, current episode moderate
- Fulfils criteria for recurrent depressive disorder
- Current episode fulfils criteria for moderate depressive episode
- At least 2 episodes lasted a minimum of 2 weeks, and were separated by several months without significant mood disturbance

Recurrent depressive disorder, current episode severe with/without psychotic symptoms
- Fulfils criteria for recurrent depressive disorder
- Current episode fulfils criteria for severe depressive episode with/without psychotic symptoms
- At least 2 episodes lasted a minimum of 2 weeks, and were separated by several months without significant mood disturbance

Recurrent depressive disorder, currently in remission
- Criteria for recurrent depressive disorder were fulfilled in the past
- Current state does not fulfill the criteria for a depressive episode of any severity, or of any other mood disorder
- At least 2 episodes lasted a minimum of 2 weeks, and were separated by several months without significant mood disturbance

Adapted: World Health Organization, ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: WHO; 1992

Appendix 5

POSSIBLE ORGANIC CAUSES OF DEPRESSION IN ELDERLY

Possible causes	Examples
Occult carcinoma	Carcinomas of lung or pancreas
Metabolic/endocrine causes	Hypothyroidism, hypercalcaemia, Cushing's disease
Drugs	Steroids, beta-blockers, methyldopa, clonidine, nifedipine, digoxin, L-dopa, tetrabenazine
Infection	Post-viral, myalgic encephalomyelitis, brucellosis, neurosyphilis
Organic brain disease	Space occupying lesion, dementia, Parkinson's disease

LABORATORY INVESTIGATIONS FOR DEPRESSION IN ELDERLY

Laboratory investigations for an elderly presented with depressive symptoms must be emphasised. The following laboratory investigations are recommended for patients presented with late life depression.

Investigation	First episode	Recurrence
Full blood count	Yes	Yes
Urea and electrolytes	Yes	Yes
Calcium	Yes	If indicated
Thyroid Function	Yes	If indicated or more than 12 months
B12	Yes	If indicated or more than 2 years
Folate	Yes	If indicated by nutritional state
Liver Function	Yes	If indicated (e.g. alcohol abuse)
Syphilitic serology	If clinically indicated	If indicated, if not done
CT Brain	If clinically indicated	Only if neurologically indicated
Electroencephalogram (EEG)	If clinically indicated	Only if neurologically indicated

Adapted: Ministry of Health, Malaysia. CPG Management of Major Depressive Disorder. Putrajaya: MoH; 2007

<div align="right">**Appendix 6A**</div>

<div align="center">**WHOOLEY QUESTIONS (Malay Version)**</div>

Dalam sebulan yang lepas, adakah anda terganggu oleh masalah berikut?
Over the past one month, have you been bothered by the following problems?

No	Soalan/Questions	Jawapan/ Answer
1.	Merasa murung, sedih atau tiada harapan? *Feeling down, depressed or hopeless?*	**Ya/Tidak** ***Yes/No***
2.	Kurang minat atau keseronokan dalam melakukan kerja-kerja? *Having little interest or pleasure in doing things?*	**Ya/Tidak** ***Yes/No***

Source:
1. Whooley MA, Avins AL, Miranda J, Browner WS. Case finding instruments for depression: Two questions are as good as many. J Gen Int Med. 1997;12(7):439–445
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<div align="right">**Appendix 6B**</div>

<div align="center">**PATIENT HEALTH QUESTIONNAIRE-2 (PHQ-2)**</div>

Dalam tempoh 2 minggu yang lepas, berapa kerapkali anda terganggu oleh masalah berikut?
Over the last 2 weeks, how often have you been bothered by the following problems?

No	Soalan/Questions	Skor/Score	
1.	Sedikit minat atau keseronokan dalam melakukan kerja-kerja *Little interest or pleasure in doing things*	Tidak pernah sama sekali/*Not at all* Beberapa hari/*Several days* Lebih dari seminggu/*More than half the days* Hampir setiap hari/*Nearly everyday*	0 1 2 3
2.	Kurang minat atau keseronokan dalam melakukan kerja-kerja *Having little interest or pleasure in doing things?"*	Tidak pernah sama sekali/*Not at all* Beberapa hari/*Several days* Lebih dari seminggu/*More than half the days* Hampir setiap hari/*Nearly everyday*	0 1 2 3

Source: Sherina MS, Arroll B, Goodyear-Smith F. Criterion validity of the PHQ-9 (Malay version) in a primary care clinic in Malaysia. Med J Malaysia. 2012;67(3):309-315

EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

Sila tandakan jawapan yang paling hampir bagi menggambarkan apa yang telah anda rasa anda rasakan **DALAM MASA TUJUH HARI** yang lalu dan bukan sekadar hari ini sahaja.

*Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.*

No	Soalan/Questions	Skor
1.	Saya dapat ketawa dan melihat kelucuan pada sesuatu perkara *I have been able to laugh and see the funny sides of things*	☐ Sebanyak mana biasa/*As much as I always could* ☐ Kurang daripada biasa/*Not quite so much now* ☐ Sangat kurang daripada biasa/*Definitely not so much now* ☐ Tiada langsung/*Not at all*
2.	Saya menanti dengan penuh harapan bagi mendapat kenikmatan apabila melakukan sesuatu perkara *I have look forward with enjoyments to things*	☐ Sebanyak mana biasa/*As much as I ever did* ☐ Kurang daripada biasa/*Rather less than what I used to do* ☐ Sangat kurang daripada biasa/*Definitely less than I used to do* ☐ Tiada langsung/*Hardly at all*
3.*	Saya menyalahkan diri sendiri secara tidak sepatutnya apabila sesuatu yang tidak kena terjadi *I have blamed myself unnecessarily when things went wrong*	☐ Ya, sepanjang masa/*Yes, most of the time* ☐ Ya, kadangkala/*Yes, some of the time* ☐ Jarang sekali/*Not very often* ☐ Tiada pernah/*No, never*
4.	Saya berasa risau atau bimbang tanpa sebab *I have been anxious or worried for no good reason*	☐ Tidak langsung/*No, no at all* ☐ Amat jarang sekali/*Hardly ever* ☐ Ya, kadangkala/*Yes, sometimes* ☐ Ya, sangat kerap/*Yes, very often*
5.*	Saya berasa takut atau panik tanpa sebab *I have felt scared pr panicky for no good reason*	☐ Ya, sangat kerap/*Yes, quite a lot* ☐ Ya, kadangkala/*Yes, sometimes* ☐ Jarang sekali/*No, not so much* ☐ Tidak pernah/*No, not at all*
6.*	Saya dibebani oleh terlalu banyak masalah *Things have been getting on top of me*	☐ Ya, kebanyakan masa saya tidak berupaya menanganinya langsung/*Yes, most of the time I haven't been able to cope at all* ☐ Ya, kadangkala saya tidak berupaya menanganinya seperti biasa/*Yes, sometimes I haven't been coping as well as usual* ☐ Tidak, kebanyakan masa saya berupaya menanganinya dengan baik/*No, most of the time I have coped quite well* ☐ Tiada, saya berupaya menangani semua masalah dengan baik pada setiap masa/*No, I have been coping as well as ever*

No	Soalan/Questions	Skor
7.*	Saya berasa sungguh sedih sehingga saya mengalami kesukaran untuk tidur *I have been so unhappy that I have had difficulty sleeping*	☐ Kebanyakan masa/*Yes, most of the time* ☐ Kadang-kadang/*Yes, sometimes* ☐ Jarang-jarang sekali/*Not very often* ☐ Tidak pernah/*No, not at all*
8.*	Saya berasa sedih atau serabut *I have felt sad or miserable*	☐ Ya, kebanyakan masa/*Yes, most of the time* ☐ Ya, agak kerap/*Yes, quite often* ☐ Jarang-jarang sekali/*Not very often* ☐ Tidak pernah *No, never*
9.*	Saya berasa sangat sedih sehingga saya menangis *I have been so unhappy that I have been crying*	☐ Ya, kebanyakan masa/Yes, most of the time ☐ Ya, agak kerap/Yes, quite often ☐ Hanya sekali sekala/Only occasionally ☐ Tidak pernah/No, never
10.*	Pernah terlintas di fikiran saya keinginan untuk mencederakan diri sendiri *The thought of harming myself has occured to me*	☐ Ya, kebanyakan masa/Yes, quite often ☐ Ya, agak kerap/Sometimes ☐ Amat jarang sekali/Hardly ever ☐ Tidak pernah/Never

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PEMARKAHAN
SCORING

SOALAN 1, 2 & 4 (tanpa *) diberi skor 0, 1, 2 atau 3 di mana kotak paling atas adalah 0 dan kotak paling bawah adalah 3.
*QUESTIONS 1, 2, & 4 (without an *) Are scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3.*

SOALAN 3, 5-10 (dengan *) diberi skor terbalik di mana kotak paling atas adalah 3 dan kotak paling bawah adalah 0.
*QUESTIONS 3, 5-¬10 (marked with an *) Are reverse scored, with the top box scored as a 3 and the bottom box scored as 0.*

Markah tertinggi: 30
Maximum score: 30

Cut-off EPDS versi Bahasa Melayu: ≥ 12
Cut-off for Malay version of EPDS: ≥ 12

Sila buat penilaian risiko bunuh diri jika soalan 10 > 0
Please assess suicidal risks if question 10 > 0

Source:
1. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. British Journal of Psychiatry. 1987;150:782-786
2. Wisner KL, Parry BL, Piontek CM. Postpartum Depression N Engl J Med. 2002;347(3):194-199
3. Abdul Kadir A, Nordin R, Ismail S, et al. Validation of the Malay Version of Edinburgh Postnatal Depression Scale for Postnatal Women in Kelantan, Malaysia. Asia Pac. Fam. Med. 2004;3 (1-2):9-18

Appendix 8

SUGGESTED ANTIDEPRESSANT DOSAGES AND ADVERSE EFFECTS

Name	Starting dose (mg/day)	Usual dose range (mg/day)	Main adverse effects	Pregnancy Category
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram	20	20 - 40	Nausea, vomiting, headache, constipation, insomnia, dry mouth, somnolence, sweating, hip fracture, dizziness, tremor, hyponatraemia, haemorrhage or bleeding, prolonged QT interval	C
Escitalopram	10	10 - 20	Nausea, diarrhoea, abdominal pain, headache, constipation, insomnia, somnolence, tremor, haemorrhage, sexual dysfunction (male and female), hyponatraemia, prolonged QT interval	C
Fluoxetine	20	20 - 60	Nausea, diarrhoea, headache, constipation, dry mouth, insomnia, somnolence, vomiting, tremor, anxiety, GI haemorrhage, rash, anorexia, hyponatremia	C
Fluvoxamine	50 - 100	50 - 300	Nausea, diarrhoea, dry mouth, insomnia, somnolence, agitation, sweating, anorexia	C
Paroxetine	20	20 - 50	Nausea, diarrhoea, headache, constipation, somnolence, insomnia, dizziness, blurred vision	D
Sertraline	50	50 - 200	Nausea, vomiting, diarrhoea, headache, constipation, insomnia, dry mouth, somnolence, dizziness, tremor, fatigue, GI haemorrhage, hyponatremia, male sexual dysfunction	C

Name	Starting dose (mg/day)	Usual dose range (mg/day)	Main adverse effects	Pregnancy Category
Serotonin and noradrenaline reuptake inhibitors (SNRIs)				
Duloxetine	20 - 60	60 - 120	Hypertension, dizziness, constipation, dry mouth, insomnia, somnolence, nausea, anorexia, sexual dysfunction, hyponatraemia, hepatic failure with or without jaundice	C
Venlafaxine	37.5 - 75	75 - 225 (up to 375 mg for in-patients)	Hypertension, headache, dizziness, constipation, dry mouth, insomnia, somnolence, nausea, anorexia, sexual dysfunction, hyponatremia, sweating, blurred vision, anxiety, elevation of blood pressure at higher doses	C
Desvenlafaxine	50	50 - 400	Hypertension, dizziness, constipation, dry mouth, insomnia, somnolence, nausea, sexual dysfunction, hyponatraemia, sweating, decreased appetite, anxiety	C
Noradrenergic and specific serotonergic antidepressant (NaSSA)				
Mirtazapine	15	15 - 45	Constipation, weight gain, dry mouth, oedema, dizziness, increased liver enzyme levels, jaundice, somnolence, hyponatraemia	C
Melatonergic agonist and serotonergic antagonist				
Agomelatine	25	25 - 50	Increased liver enzymes, constipation, nausea, diarrhoea, vomiting, abdominal pain, dry mouth, headache, dizziness, insomnia, somnolence, fatigue, jaundice, tremor, agitation, blurred vision	B
Multimodal serotonin modulator				
Vortioxetine	10	10 - 20	Constipation, nausea, diarrhoea, vomiting, dry mouth, night sweating, dizziness, sexual dysfunction	B
Noradrenaline and dopamine reuptake inhibitors (NDRIs)				
Bupropion	150	150 - 400	Constipation, abdominal pain, nausea, headache, dizziness, somnolence dry mouth, insomnia, tachycardia, rash, tinnitus, tremor	C

Name	Starting dose (mg/day)	Usual dose range (mg/day)	Main adverse effects	Pregnancy Category
Tricyclic and tetracyclic antidepressants (TCAs)				
Amitriptyline	50 - 75	75 - 150 (up to 300 mg for in-patients)	Constipation, hypotension, tachycardia, arrhythmias, dizziness, drowsiness, tremor, dry mouth, blurred vision, urinary retention, weight gain, fatigue, prolonged QT interval	C
Clomipramine	10 - 75	30 - 150 (up to 250 in severe cases)	Constipation, postural hypotension, dizziness, headache, tremor, dry mouth, nausea, fatigue, somnolence, sexual dysfunction, prolonged QT interval	C
Dothiepin	50 - 75	75 - 225	Constipation, hypotension, postural hypotension, drowsiness, dizziness, tremor, dry mouth, blurred vision, urinary retention, tachycardia, increased or decreased libido	C
Imipramine	25 - 50	50 - 200 (up to 300 mg for in-patients)	Constipation, postural hypotension, dizziness, headache, dry mouth, blurred vision, urinary retention, prolonged QT interval, cardiac conduction disturbance	C
Mianserin	30	30 - 90	Tachycardia, dizziness, drowsiness, vomiting, gynaecomastia, convulsions	B
Nortriptyline	75 - 100	75 - 150	Constipation, postural hypotension, dry mouth, blurred vision, urinary retention, elevation or reduction of blood sugar levels, prolonged QT interval, cardiac conduction disturbance	C
Monoamine oxidase inhibitors (MAOIs)				
Phenelzine	15	30	Hypertensive crisis which has been associated with intracranial bleeding, postural hypotension, arrhythmias, headache, abdominal discomfort, constipation, weight gain, dry mouth, somnolence, erectile dysfunction	B
Moclobemide	150	150 - 600	Hypertensive crisis, tachycardia, dizziness, headache, abdominal pain, nausea, diarrhoea, vomiting, sleep disturbances, constipation, somnolence, agitation, anxiety, increased appetite, blurred vision	B

UNITED STATES FOOD AND DRUG ADMINISTRATION (FDA) PREGNANCY RISK CATEGORIES

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the foetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Adapted:

1. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines In Psychiatry Eleventh Edition. West Sussex; Wiley Blackwell: 2012
2. Micromedex® Solution (Available at: http://www.micromedexsolutions.com/micromedex2/4.24.0/WebHelp/MICROMEDEX_2.htm)
3. Mims Online (Available at: https://www.mims.com/)
4. Kennedy SH, Lam RW, McIntyre RS, et al. CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016;61(9):540-560
5. Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;(7):CD008242
6. Plesničar BK. Efficacy and tolerability of agomelatine in the treatment of depression. Patient Prefer Adherence. 2014;8:603–612

LIST OF ABBREVIATIONS

AAP(s)	atypical antipsychotic(s)
AED(s)	antiepileptic drug(s)
AGREE	Appraisal of Guidelines for Research and Evaluation
BDI	Beck Depression Inventory
BT	Behavioural Therapy
CBT	cognitive behavioural therapy
CPG(s)	clinical practice guidelines
CI	confidence interval
CV	cardiovascular
DASS	Depression, Anxiety and Stress Scale
DG	development group
DMT	dance movement therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	electroconvulsive therapy
ES	effect size
EPDS	Edinburgh Postnatal Depression Scale
GDS	Geriatric Depression Scale
GI	gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HADS	Hospital Anxiety Depression Scale
HAM-D	Hamilton Depression Rating Scale
HTA	Health Technology Assessment
HR	hazard ratio
iCBT	internet-based cognitive behavioural therapy
ICD	International Statistical Classification of Diseases and Related Health Problems
IPT	interpersonal therapy
IQR	interquartile range
IV	intravenous
MADRS	Montgomery-Asberg Depression Rating Scale
MaHTAS	Malaysian Health Technology Assessment Section
MAOI(s)	monoamine oxidase inhibitors
MBCT	mindfulness-based cognitive therapy
MDD	major depressive disorder
MD	mean difference
MMSE	Mini Mental State Examination
NNT	number needed to treat
OR	odds ratio
p	p value
PHQ-9	Patient Health Questionnaire-9
PST	problem-solving therapy
RCT(s)	randomised controlled trial(s)
RR	relative risk
rTMS	repetitive transcranial magnetic stimulation
SMD	standardized mean difference
SNRIs	serotonin noradrenaline reuptake inhibitors
SR	systematic review
SSRIs	selective serotonin reuptake inhibitors
STPP	short-term pychodynamic psychotherapy
TAU	treatment as usual

TCAs	tricyclic antidepressants
tDCS	transcranial direct current stimulation
TRD	treatment-resistant depression
USPSTF	US Preventive Services Task Force
YLD	Years Lived with Disability
5HT2c	5HT2c receptor
WHO	World Health Organization