### Table 2: Ongoing Monitoring During Treatment of MDD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Agent</th>
<th>Frequency of Monitoring</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>At baseline &amp; at 6-monthly</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>At baseline, with significant dose increase &amp; 3 to 6-monthly after stabilisation</td>
<td></td>
</tr>
<tr>
<td>Electrocardiogramme</td>
<td></td>
<td></td>
<td>For QT prolongation</td>
</tr>
<tr>
<td></td>
<td>TCA</td>
<td>At baseline, after initial dose titration &amp; at change of dose</td>
<td>In individuals over 45 years of age or with cardiovascular (CV) disorders</td>
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<tr>
<td></td>
<td>MAOI</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Closer monitoring of MAOIs in first weeks until tolerance occurs</td>
<td></td>
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<tr>
<td>Liver function test</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>SNRI</td>
<td>At baseline In individuals with CV risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SSRIs</td>
<td>At baseline, 3, 6, 12 &amp; 24 weeks after initiation dosage, after dosage increment or when clinically indicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment should be discontinued if transaminases exceed three times upper limit of normal</td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SSRIs</td>
<td>At baseline &amp; at 1 month after treatment initiation or clinically indicated in high risk groups*</td>
<td>More frequent monitoring in elderly or those with existing hyponatraemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Need to monitor together with urine &amp; serum osmolality since SSRIs can induce hypovolemic hyponatremia via Syndrome of Inappropriate Antidiuretic Hormone Secretion</td>
<td></td>
</tr>
<tr>
<td>Full blood count</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>SNRI</td>
<td>To detect blood dyscrasia (e.g. neutropenia &amp; thrombocytopaenia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SSRIs</td>
<td>As clinically indicated in high risk groups for osteoporosis** Refer to Fracture Risk Assessment Tool Score in Ministry of Health CPG Management of Osteoporosis, 2012</td>
<td></td>
</tr>
<tr>
<td>Bone mineral density</td>
<td></td>
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</tr>
</tbody>
</table>
1. Major Depressive Disorder (MDD) is characterised by persistent low mood, loss of interest, difficulty in concentrating, sleep disturbances, fatigue & in more severe form, functional impairment & suicidal ideations.

2. Screening for depression using Whooley Questions in primary care may be considered in people at risk (refer to Screening & Assessment).

3. Screening for perinatal depression may be done in two-stage approach. Use brief screening tools e.g. Patient Health Questionnaire-2 or Whooley Questions in the first stage & followed by Edinburgh Postnatal Depression Scale.

4. Psychoeducation should be offered early & continuously throughout the management of MDD.

5. Psychosocial interventions & psychotherapy should be offered throughout all severity, while combination of pharmacological intervention & psychotherapy should be offered in moderate to severe MDD.

6. Second-generation antidepressants may be considered as the initial treatment medication, while the older antidepressants e.g. tricyclic antidepressants (TCAs) & monoamine oxidase inhibitors (MAOIs) are considered for subsequent choice (refer to Table 1).

7. Short-term benzodiazepines (not more than 2 - 4 weeks) may be used in MDD with anxiety, agitation or insomnia.

8. Antidepressants should be continued for at least 6 - 9 months after remission & at least 2 years if there is high risk of relapse or recurrence.

9. Women in their reproductive age with MDD should receive pre-pregnancy care. Benefits & risks of treatment to mother & baby in both short- & long-term; & possible consequences of no treatment or if treatment is changed or stopped abruptly should be considered throughout perinatal period (refer to Algorithm 2).

10. Monitoring requirements for some drugs are needed (refer to Table 2).

This Quick Reference provides key messages & a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Major Depressive Disorder (Second Edition).

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:

Ministry of Health Malaysia: www.moh.gov.my

Academy of Medicine Malaysia: www.acadmed.org.my

Malaysian Psychiatric Association: www.psychiatry-malaysia.org/

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**CLINICAL PRACTICE GUIDELINES SECRETARIAT**

Malaysian Health Technology Assessment Section (MaHTAS)

Medical Development Division, Ministry of Health Malaysia

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Federal Government Administrative Centre 62590

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E-mail: htamalaysia@moh.gov.my
SCREENING & ASSESSMENT

Screening for MDD should be done in high risk individuals* using the following tool:

- **Whooley Questions on depression:**
  1. "During the past month, have you often been bothered by feeling down, depressed or hopeless?"
  2. "During the past month, have you often been bothered by having little interest or pleasure in doing things?"

*High risk individuals are:
- first-degree relative with history of depression
- chronic pain (e.g. backache, headache)
- experiencing major life changes
- multiple vague symptoms
- loss of interest in sexual activity
- chronic diseases
- impoverished home environment
- pregnant or postpartum period
- sleep disturbance
- old age
- obesity
- financial constrain
- socially-isolated
- substance abuse e.g. alcohol, illicit drugs

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.

- The severity of MDD should be assessed to determine the mode of treatment.

REFERRAL CRITERIA

- In local setting, referral to the psychiatric services may be done through the emergency & trauma department or directly to the psychiatric clinic. Indications for referral to psychiatric services include:
  - unsure of diagnosis
  - attempted suicide
  - active suicidal ideas
  - failure of treatment
  - advice on further treatment
  - clinical deterioration
  - recurrent episode within 1 year
  - psychotic symptoms
  - severe agitation
  - self-neglect
ALGORITHM 1. TREATMENT OF MAJOR DEPRESSIVE DISORDER

QUICK REFERENCE FOR HEALTHCARE PROVIDERS
MANAGEMENT OF MAJOR DEPRESSIVE DISORDER (SECOND EDITION)

TREATMENT

ACUTE
• Mild To Moderate
  • In mild to moderate MDD, psychosocial intervention & 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 MDD, a combination of pharmacotherapy & psychotherapy should be offered.
  • In moderate to severe MDD, exercise may be offered as an adjunct treatment.
  • In moderate to severe MDD, 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 & CONTINUATION PHASE
• Antidepressants should be continued for at least 6 - 9 months after remission, & at least 2 years if there is high risk of relapse or recurrence.

ECT = electroconvulsive therapy

FIGURE 1. PHASES OF TREATMENT OF MAJOR DEPRESSION

Continuation and maintenance
Acute
Symptoms
"Normalcy"
Treatment Phases
Syndrome
Response
Remission
Relapse
Recovery
Recurrence
Progression to Disorder

X
X

DIAGNOSIS

To achieve remission

Phases of treatment

To prevent relapse, recurrence and development of chronicity

CONTINUATION AND MAINTENANCE

Pharmacotherapy + Psychosocial intervention

Pharmacotherapy + Psychotherapy + Psychosocial intervention

Pharmacotherapy + Psychotherapy

Pharmacotherapy
ACUTE PHASE

- Mild To Moderate

- Moderate To Severe

MAINTENANCE & CONTINUATION PHASE
SCREENING & ASSESSMENT

Screening for MDD should be done in high risk individuals* using the following tool:

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  1. “During the past month, have you often been bothered by feeling down, depressed or hopeless?”
  2. “During the past month, have you often been bothered by having little interest or pleasure in doing things?”

*High risk individuals are:

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  - attempted suicide
  - active suicidal ideas
  - failure of treatment
  - advice on further treatment
  - clinical deterioration
  - recurrent episode within 1 year
  - psychotic symptoms
  - severe agitation
  - self-neglect
  - first-degree relative with history of depression
  - chronic pain (e.g. backache, headache)
  - experiencing major life changes
  - multiple vague symptoms
  - loss of interest in sexual activity
  - chronic diseases
  - impoverished home environment
  - pregnant or postpartum period
  - sleep disturbance
  - old age
  - obesity
  - financial constrain
  - socially-isolated
  - substance abuse e.g. alcohol, illicit drugs

QUICK REFERENCE FOR HEALTHCARE PROVIDERS
MANAGEMENT OF MAJOR DEPRESSIVE DISORDER (SECOND EDITION)

### TABLE 1. COMMONLY USED ANTIDEPRESSANTS, DOSAGES & ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Usual dose range (mg/day)</th>
<th>Usual dose range (mg/day)</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10 - 20</td>
<td>10 - 20</td>
<td>Nausea, diarrhoea, headache, constipation, dry mouth, insomnia, somnolence</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 - 60</td>
<td>20 - 60</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 - 200</td>
<td>50 - 200</td>
<td></td>
</tr>
<tr>
<td><strong>Serotonin &amp; noradrenaline reuptake inhibitors (SNRIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>20 - 60</td>
<td>20 - 60</td>
<td>Hypertension, dizziness, constipation, dry mouth, somnolence, nausea, sexual dysfunction</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 - 75 (up to 375 mg for in-patients)</td>
<td>75 - 225 (up to 375 mg for in-patients)</td>
<td>Constipation, weight gain, dry mouth, oedema, dizziness, increased liver enzyme levels, dizziness, fatigue, jaundice, tremor, agitation, blurred vision</td>
</tr>
<tr>
<td><strong>Noradrenergic &amp; specific serotonin antidepressant (NaSSA)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mirtazapine</td>
<td>15</td>
<td>15</td>
<td>Constipation, weight gain, dry mouth, oedema, dizziness, increased liver enzyme levels, jaundice, somnolence, hypotension</td>
</tr>
<tr>
<td><strong>Melatonergic agonist &amp; serotonergic antagonist</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agomelatine</td>
<td>25</td>
<td>25</td>
<td>Increased liver enzymes, constipation, nausea, diarrhoea, vomiting, abdominal pain, dry mouth, headache, dizziness, insomnia, somnolence, fatigue, jaundice, tremor, agitation, blurred vision</td>
</tr>
<tr>
<td><strong>Multimodal serotonin modulator</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>10</td>
<td>10</td>
<td>Constipation, nausea, diarrhoea, vomiting, dry mouth, right sweating, dizziness, sexual dysfunction</td>
</tr>
<tr>
<td><strong>Tricyclics &amp; tetracyclic antidepressants (TCAs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitryptiline</td>
<td>50 - 75</td>
<td>75 - 150</td>
<td>Constipation, hypersomnia, hiccups, dizziness, insomnia, somnolence, blurred vision, palpitations, tremor, dry mouth, dizziness, sexual dysfunction</td>
</tr>
<tr>
<td>Dothiepin</td>
<td>50 - 75</td>
<td>75 - 225</td>
<td>Constipation, weight gain, dry mouth, oedema, dizziness, increased liver enzyme levels, headache, somnolence, nausea, sexual dysfunction</td>
</tr>
<tr>
<td>Imipramine</td>
<td>50 - 200</td>
<td>75 - 225</td>
<td>Constipation, weight gain, dry mouth, oedema, dizziness, increased liver enzyme levels, headache, somnolence, nausea, sexual dysfunction</td>
</tr>
<tr>
<td><strong>Monoamine oxidase inhibitors (MAOIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moclobemide</td>
<td>50 - 600</td>
<td>50 - 600</td>
<td>Hypertensive crisis, lightheadedness, dizziness, headache, abdominal pain, nausea, diarrhoea, vomiting, sleep disturbances, constipation, somnolence, agitation, blurred vision, appetite, blurred vision</td>
</tr>
</tbody>
</table>

Pregnancy Category

- C: Pregnancy category C
- B: Pregnancy category B
- A: Pregnancy category A
- D: Pregnancy category D
ALGORITHM 2. TREATMENT OF PRE-EXISTING MAJOR DEPRESSIVE DISORDER IN PRE-PREGNANCY, PREGNANCY & POSTPARTUM PERIOD

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

Mild MDD not on antidepressant

Moderate - Severe MDD

On antidepressant

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

Continue antidepressant

Consider combination with psychotherapy

Switch antidepressant

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

Stop antidepressant

Expedit e psychotherapy with close monitoring of symptoms

Not on antidepressant

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

Start antidepressant

Consider combination with psychotherapy

No antidepressant

Expedit e psychotherapy with close monitoring of symptoms
**FOLLOW-UP & MONITORING**

**TABLE 2. ONGOING MONITORING DURING TREATMENT OF MDD**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Agent</th>
<th>Frequency of the monitoring parameter</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index &amp; waist circumference</td>
<td>NASSAs MAOIs TCAs</td>
<td>At baseline &amp; at 6-monthly</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Venlafaxine TCAs MAOIs</td>
<td>At baseline, with significant dose increase &amp; 3 to 6-monthly after stabilisation</td>
<td>Closer monitoring of MAOIs in first weeks until tolerance occurs</td>
</tr>
<tr>
<td>Electro-cardiogramme for QT prolongation</td>
<td>TCAs</td>
<td>At baseline, after initial dose titration &amp; at change of dose</td>
<td>In individuals over 45 years of age or with cardiovascular (CV) disorders</td>
</tr>
<tr>
<td></td>
<td>SNRIs SSRIs</td>
<td>At baseline</td>
<td>In individuals with CV risk</td>
</tr>
<tr>
<td>Liver function test</td>
<td>Agomelatine</td>
<td>At baseline, 3, 6, 12 &amp; 24 weeks after initiation dosage, after dosage increment or when clinically indicated</td>
<td>Treatment should be discontinued if transaminases exceed three times upper limit of normal</td>
</tr>
</tbody>
</table>
| Electrolytes | SSRIs Mirtazapine SNRIs TCAs | At baseline & at 1 month after treatment initiation or clinically indicated in high risk groups* | • More frequent monitoring in elderly or those with existing hyponatraemia  
• Need to monitor together with urine & serum osmolality since SSRIs can induce hypovolemic hyponatraemia via Syndrome of Inappropriate Antidiuretic Hormone Secretion |
| Full blood count | Mirtazapine Mianserin | If clinically indicated | To detect blood dyscrasia (e.g. neutropenia & thrombocytopenia) |
| Bone mineral density | SSRIs | As clinically indicated in high risk groups for osteoporosis** | Refer to Fracture Risk Assessment Tool Score in Ministry of Health CPG Management of Osteoporosis, 2012 |

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