ACE CLINICAL GUIDELINE

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# Major depressive disorder

## Achieving and sustaining remission

| Objective | Scope | Target audience |
|---|---|---|
| To enhance long-term management of major depressive disorder (MDD), for achieving remission and reducing relapse | Non-pharmacological and pharmacological management of MDD in adults, during the acute and maintenance phases of treatment | This clinical guideline is relevant to all healthcare professionals caring for patients with diagnosed MDD, especially those in primary or generalist care |

Major depressive disorder (MDD) is highly debilitating. Patients experience a reduction in quality of life[1] and ability to function,[2] impacting interpersonal relationships, education, and employment.[3–5] This may result in an overall substantial economic impact (due to demands on healthcare utilisation and reduced productivity).[5, 6] The numerous detrimental effects of this mental health condition, including the increased likelihood of suicidal behaviour,[7] underscore the need for effective treatments.

The 2023 National Mental Health and Well-being Strategy aims to enhance primary care capacity and capability for managing mental health conditions, which will facilitate anchoring care in community settings under a tiered care model.[8] In support of the National Strategy, this ACE Clinical Guideline (ACG) aims to inform clinical management of MDD in primary and generalist care, among patients with a diagnosis of MDD. See Figure 1 for an overview of MDD management. Adults (patients 18 years old and above) are the focus of this ACG, though brief guidance on other populations is also included. Depression and anxiety are commonly comorbid[9] – management of generalised anxiety disorder (GAD) is covered in another ACG.

**Statement of Intent**

This ACE Clinical Guideline (ACG) provides concise, evidence-based recommendations and serves as a common starting point nationally for clinical decision-making. It is underpinned by a wide array of considerations contextualised to Singapore, based on best available evidence at the time of development. The ACG is not exhaustive of the subject matter and does not replace clinical judgement. The recommendations in the ACG are not mandatory, and the responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.

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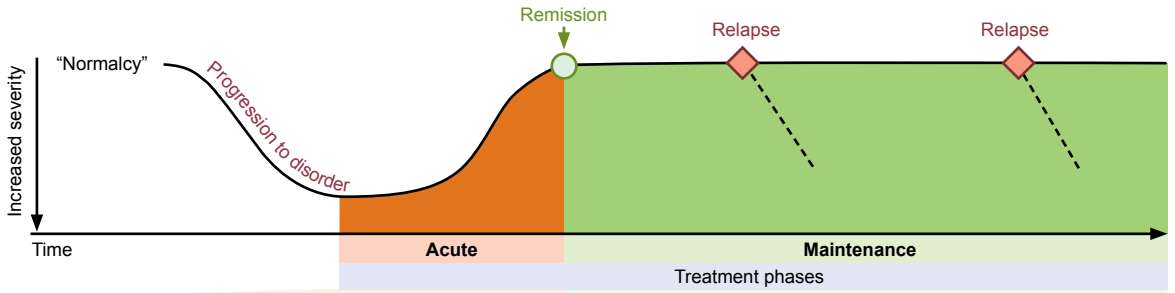
College of Psychiatrists

**Figure 1.** Overview of MDD management

An MDD episode is characterised by a period of at least two weeks in which a depressed mood and/or diminished interest or pleasure in activities are experienced nearly every day, alongside other symptoms (changes in weight or appetite, disruption to normal sleep patterns, psychomotor agitation or retardation, loss of energy, reduced ability to think or concentrate, feelings of worthlessness or excessive guilt, and recurrent thoughts of death or suicide)[4,5] Patient's quality of life and functioning are significantly impacted.[2]

The management goal for MDD is to **achieve and sustain remission**, which includes relief from symptoms and restoration of functioning.[10]

Treatment for patients with diagnosed MDD* entails both an **acute** phase (to treat the presenting episode) and a **maintenance** phase (to prevent relapse).[10,†]




Involvement of specialist care may be considered at various junctures in the patient journey. See *referral considerations* notepads for further details.

**Aim:** To restore function and resolve symptoms (since remission of symptoms is associated with reduced risk of relapse)[10,11]

*See section:* **Assessment to guide management**

Evaluate MDD severity based on symptom profile, functional impairment, and risk of harm (**Recommendation 1**).

*See **Figures 3a, 3b** for further details.*

Personalise the treatment approach based on MDD severity and other patient factors (**Recommendation 2**).

*See section:* **Treatment of an MDD episode**

For patients with mild to moderate MDD

Offer psychological treatment over antidepressants where feasible and acceptable (**Recommendation 3**).

For patients with moderately severe or severe MDD

Offer a combination of a second-generation antidepressant with psychotherapy, or psychotherapy alone. When psychotherapy is not feasible or acceptable, consider a second-generation antidepressant (**Recommendations 4a, 4b**).

*See **Table 1** for key considerations in selecting a second-generation antidepressant. When initiating antidepressant therapy, start at a low dose.*

Assess treatment response after an adequate treatment trial (about 4 to 12 weeks of antidepressant at appropriate therapeutic dose and/or about 8 to 9 sessions of psychotherapy).

Treatment response is suboptimal (for example, <50% reduction in depression symptom scores)

Assess possible reasons for suboptimal treatment response (**Recommendation 5**).

Where possible, address reasons for treatment ineffectiveness.

Treatment response remains suboptimal

A change in management strategy may be required.

*See **Figure 4** for recommended strategies.*

Treatment response remains suboptimal

Patient may benefit from referral to specialist services.

Treatment response elicited

Treatment response elicited

Treatment response elicited

Continue treatment till **remission** is reached

- Monitoring for remission of symptoms may be operationalised using threshold scores on depression symptom scales, such as a score of less than five on the nine-item Patient Health Questionnaire (PHQ-9).[10,12]
- Full remission of symptoms may not always be viable for all patients, for example those with persistent depression[10] or with limited life expectancy. In such cases, treatment may focus on reducing depression symptoms or increasing quality of life as much as possible.

**Aim:** sustain remission and reduce risk of relapse

*See section:* **Management to reduce risk of relapse**

Continue treatment after remission to reduce relapse risk; if antidepressants are prescribed, continue at optimal dose for at least 6 months after remission (**Recommendation 6**).

Effective treatments for reducing relapse risk:[13–15]

- Continuation of antidepressant treatment
- Provision of psychological treatment (effective even with tapering of antidepressants)
- Combination of psychological treatment and antidepressants

*[For patients on antidepressants]* After 6 months of maintenance antidepressant treatment

Initiate a conversation with the patient for shared decision-making regarding further continuation of antidepressants.

*See **Figure 5** for key factors to consider when deciding to continue or discontinue antidepressants after 6-month maintenance treatment.*

Continue antidepressant treatment.

Discontinue antidepressant treatment.

*Minimise discontinuation symptoms by gradually reducing (tapering) the antidepressant dose.*

Monitor and reassess patient as needed.

Note: This ACG focuses on adults (patients 18 years old and above), with brief guidance on other populations included:

- Perinatal populations – Supplement 1
- Children and adolescents – Supplement 2
- Other special populations – page 11

* Screening and diagnosis of MDD is not covered in this ACG's scope. For details on diagnostic assessment of MDD, clinicians may refer to the latest Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases.

† Some international guidelines describe three phases in MDD treatment: acute, continuation (post-remission; relapse may occur), and maintenance (post-recovery; recurrence may occur).[16,17] Others have combined the latter two phases,[10,18] acknowledging a lack of empirical differentiation between relapse and recurrence.[10] This ACG adopts a two-phase treatment approach to MDD, acknowledging that the duration of maintenance treatment needs to be tailored to the individual patient (see Recommendation 6). The graph above is adapted from the Department of Veterans Affairs and Department of Defense clinical practice guideline for the management of major depressive disorder.[16]

## Assessment to guide management

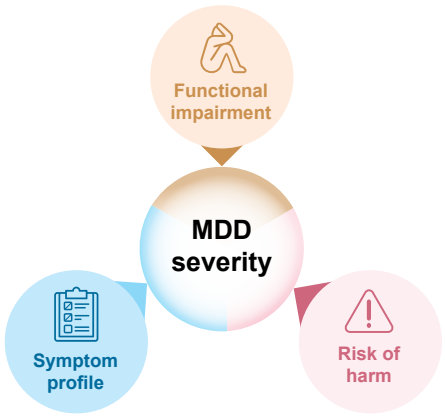
### Recommendation 1

**Evaluate MDD severity based on**

- **Symptom profile,**
- **Functional impairment, and**
- **Risk of harm (to self or others).**

For patients who have been diagnosed with MDD, the first step is to determine the severity to inform management.[16,18]

**Figure 2.** Components of MDD severity




Assessing both a patient's symptoms and extent of functional impairment provides a well-rounded view of the overall severity.[4,5,10] As patients with MDD have a greatly increased vulnerability for suicide,[7] incorporating risk of harm assessment is crucial (Figure 2). Figure 3a provides further details on each of these dimensions, and Figure 3b illustrates their interplay.

Locally, the PHQ-9 is commonly used to characterise the intensity of depression symptoms, which is a core dimension of the patient's overall symptom profile.

### Recommendation 2

**Personalise the treatment approach based on MDD severity and other patient factors.**

The assessed severity of the current MDD episode informs the intensity of treatment provided (see Recommendations 3 and 4). Other patient factors can also influence the overall treatment approach. These include:

| Patient factors | Impact on treatment approach |
|---|---|
| Patient preference | Patients may prefer either pharmacological or non-pharmacological treatment. Factor this in when selecting treatment, via shared decision-making. |
| Physical illnesses and concurrent medication | Pharmacotherapy choice and dosing is influenced by patient's comorbidities and current medication regime. For example, lower antidepressant doses may be required for patients with renal or hepatic impairment. When selecting an antidepressant, consider potential drug interactions with concurrent medications which may increase the side effect burden. Refer to package inserts or drug information references for further details. |
| Social and environmental factors | Sources of stressors can be targeted as a complement to clinical treatment. For example, referral can be made to community resources or social services for patients experiencing domestic unrest or financial pressure. |
| History of past episodes and treatment | Treatments that worked previously can be restarted.[19] |

**Figure 3a.** Evaluation of MDD severity (to inform management) is based on symptom profile, functional impairment, and risk of harm (to self or others)

### Symptom profile

Assess the presenting symptoms in terms of:

- **Intensity:** Several scales measure the intensity of depression symptoms. Locally, the nine-item Patient Health Questionnaire (PHQ-9) is commonly used. As PHQ-9 scores are derived from patient reporting, corroborate findings based on clinical judgement.
- **Duration:** A longer duration of untreated symptoms is associated with poorer prognosis[20] and therefore represents greater severity.
- **Comorbid mental health symptoms:** Co-occurring symptoms of other conditions such as anxiety, addiction, personality disorders, or psychosis tend to indicate a greater severity or more refractory depression.[5]

### Functional impairment

Dimensions of assessment include:

- Capacity for social interactions
- Ability to perform school, workplace, or household responsibilities
- Ability to care for self (for example maintaining personal hygiene)

Instruments, such as the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), may be used to facilitate assessment.

**MDD severity**

### Risk of harm

...to self:

- Check for **current suicide ideation and intent (including if any specific suicide plans)**[19]
- Additionally assess for factors that increase risk of suicide, such as:[21–24]
  - History of suicide planning or attempts (strongest association with future suicide attempts)
  - Alcohol or substance abuse
  - Adverse childhood experiences (such as emotional neglect, parental separation or death of a parent)
  - Psychosocial stressors (such as domestic abuse and financial pressure)

While various suicide risk assessment tools (such as the Columbia-Suicide Severity Rating Scale) may facilitate assessment, clinical judgement is paramount.

Consider a safety plan for patients assessed to be at risk of suicide.[10] Further details on red flags for urgent attention, suicide risk assessment, developing a safety plan and referral pathways may be found in the upcoming *Practice Guide for Tiered Care Model for Mental Health (Adult)*.

...to others:

Consider if there is any intent or risk to harm others, such as family members or caregivers. Among factors associated with harming others, having a history of aggressive behaviour has the strongest association.[25]

### Holistically evaluating MDD severity

PHQ-9 scores serve as a useful starting point for categorising MDD severity, with the other dimensions contributing to the overall clinical assessment.

| PHQ-9 score‡ | Other dimensions of MDD severity | MDD severity |
|---|---|---|
| ≤14 (typically in the range of 5 to 14) | • Duration of episode<br>• Comorbid mental health symptoms<br>• Functional impairment<br>• Risk of harm to self or others | Mild to moderate |
| 15–19 | | Moderately severe |
| 20–27 | | Severe |

### Referral considerations

Refer patients with MDD to emergency departments or tertiary care if they have:

- High risk of harm to self or others, or
- Symptoms of psychosis.

Referral may be considered for patients with severe symptoms or severe functional impairment, as required.

‡ PHQ-9 scores presented are in the context of patients who have been diagnosed with MDD (for example, based on Diagnostic and Statistical Manual of Mental Disorders). Note that for the purpose of right-siting, the upcoming *Practice Guide for Tiered Care Model for Mental Health (Adult)* recommends Tier 2 service providers (typically non-medical community mental health practitioners) refer clients with PHQ-9 score of 10 and above to Tier 3 providers (such as primary care doctors) for assessment. This ACE Clinical Guideline is scoped for clinical management of **diagnosed** MDD in primary and generalist care. Therefore, a single PHQ-9 score range of 14 and below is employed for mild to moderate MDD, in recognition that some patients may initially screen with a low PHQ-9 score yet subsequently be diagnosed with MDD upon clinical assessment. In such cases, scores of 5 to 9 may represent mild severity, and accordingly scores of 10 to 14 may represent moderate severity.

**Figure 3b.** Clinical vignettes illustrating holistic assessment of MDD severity (based on symptom profile, functional impairment, and risk of harm)

The interplay of the symptom profile, functional impairment, and risk of harm is illustrated in the clinical vignettes below: while the two patients have similar intensity of depression symptoms, greater MDD severity is assigned to Patient 2 for clinical management due to the assessment of the other domains.

**Patient 1**

32-year-old working mother who is facing considerable stress caring for her two young children, but has strong supportive network from family and friends.

- PHQ-9 score of 14 (moderate MDD), with loss of pleasure in typically-enjoyed activities and other depression symptoms.
- Symptoms have been present for 3 weeks.
- No features of other mental health conditions.
- Goes to work most days but finds it difficult to focus; maintains most social engagements.
- No suicide ideation; no intent to harm.

Managed as **moderate** MDD.

**Patient 2**

55-year-old man living alone in a small high-rise flat; currently not working; brought to clinic by daughter, who visits him occasionally; on treatment for diabetes mellitus and hypertension.

- PHQ-9 score of 12 (moderate MDD), with depressed mood and other depression symptoms.
- Symptoms have been present for the past 4 months.
- No features of other mental health conditions.
- Has not left the house for 2 months and stopped meeting his friends; frequently spends the whole day on the couch, skipping meals and not showering.
- Sometimes wishes he was dead and has history of suicide planning, but currently no active suicidal intent; no intent to harm.

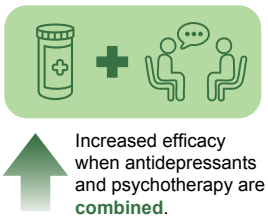
Managed as **moderately severe** MDD despite moderate PHQ-9 score, in view of long duration of untreated symptoms, marked functional impairment and risk of self-harm.

## Treatment of an MDD episode

### Evidence of efficacy and benefit-risk profile of treatments

**The mainstay treatment options for MDD in primary care are antidepressants, psychological treatment (supportive counselling or psychotherapy),[a] and a combination of both.** Network meta-analyses of randomised controlled trials (RCTs) have found that combining antidepressants with psychotherapy results in increased response[26] and remission[27] rates for depression, compared to antidepressants or psychotherapy alone. Overall, a combined treatment approach is most effective for patients with MDD, although the evidence base is more established for moderately severe and severe depression than for mild to moderate depression.[27]

While antidepressants and psychotherapy are equally efficacious, the benefit-risk balance is more favourable for psychotherapy due to risk of adverse effects with antidepressants.



Increased efficacy when antidepressants and psychotherapy are **combined**.

Antidepressant treatment and psychotherapy are equally effective in achieving remission.[27–29] There is emerging evidence that psychotherapy may be more effective in the long term, although further research is required.[26,27] Given that antidepressants and psychotherapy are equally efficacious, and considering the risk of adverse effects with antidepressant use,[18,28] the overall benefit-risk balance is more favourable for psychotherapy.

**Recommendation 3** **For patients with mild to moderate MDD, offer psychological treatment over antidepressants where feasible and acceptable.**

### Preferred treatment of mild to moderate MDD

**Psychological treatments (supportive counselling or psychotherapy) are preferred over antidepressants for mild to moderate MDD.** Supportive counselling has proven to reduce depression symptoms, although it may be less efficacious than psychotherapy.[30]

In circumstances where these are not acceptable to the patient or not feasible, antidepressants may be required. For example:

- The healthcare professional assesses a need for, or the patient prefers, initiating treatment sooner (than waiting time allows)
- The healthcare professional assesses that some symptomatic improvement is required before the patient can adequately engage in psychological treatment
- The patient is unwilling to engage in psychological treatment
- The patient is unable to attend or commit to regular therapy sessions
- The patient is unable to participate in or understand tasks for therapy sessions (for example, due to cognitive impairment)

As MDD severity is dynamic, antidepressants can be started pre-emptively to supplement psychological treatment if clinical assessment indicates that the patient's symptoms may worsen soon.

If referring to another healthcare professional for counselling or psychotherapy, provide information on MDD severity and other patient factors evaluated (Recommendations 1 and 2). Selection and delivery of an evidence-based psychotherapy is tailored to the patient's therapeutic needs and preferences (see notepad *Selecting and delivering psychotherapy for MDD* on the next page for more information on evidence-based psychotherapies and delivery formats).

[a] In this ACG, psychological treatment is used as an umbrella term to include both psychotherapy and supportive counselling. Psychotherapies are structured upon specific objectives (for example, cognitive behavioural therapy guides patients in identifying the impact of their thought patterns and actions on their emotions and behaviours). Supportive counselling tends to be more unstructured, focusing on listening skills and developing a robust therapeutic alliance with the patient.[16]

### Selecting and delivering psychotherapy for MDD

#### Choice of psychotherapy

Various psychotherapies have proven efficacy in RCTs, with no significant differences between them. These include:[31–33]

- Behavioural activation therapy
- Cognitive behavioural therapy
- Interpersonal therapy
- Problem-solving therapy
- Psychodynamic therapy
- Schema therapy
- Third-wave therapies (for example, mindfulness-based cognitive therapy, acceptance and commitment therapy, and positive psychotherapy)

#### Delivery formats

Various formats of administering psychotherapy have been found to be equally efficacious, including:[34]

- Individual therapy
- Group therapy
- Telephone-delivered therapy
- Guided internet-delivered therapy

Guided internet-delivered therapy is an emerging treatment format for MDD: psychotherapy materials are provided for the patient to work through, with guidance from a trained professional.[16] Current evidence indicates that this treatment format is effective for treating depression, although treatment dropout may be higher compared to the other delivery formats. Unguided internet-delivered therapy has not proven efficacious for treatment of depression.[34]

**Recommendation 4**

**For patients with moderately severe or severe MDD:**

**a) Offer a combination of a second-generation antidepressant with psychotherapy, or psychotherapy alone.**

**b) Consider a second-generation antidepressant when psychotherapy is not feasible or acceptable.**

## Preferred treatment of moderately severe and severe MDD

Combining a second-generation antidepressant with psychotherapy, or psychotherapy alone, are preferred for treating moderately severe and severe MDD, given greater efficacy and more favourable benefit-risk balance respectively (Recommendation 4a). Nonetheless, similar to mild to moderate MDD, some patients may be unwilling or unable to engage in psychotherapy. In these cases, treatment with a second-generation antidepressant on its own is an accepted alternative (Recommendation 4b). **Co-management or referral to a specialist may be required, especially for severe MDD, depending on the healthcare professional's experience.**

### First and second-generation antidepressants

First-generation antidepressants refer to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), while second-generation antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and other newer agents.

Second-generation antidepressants are recommended as the first-line antidepressants for treatment of MDD.[16,18,19] First-generation antidepressants are not preferred for routine use[16,18,19] due to their low therapeutic index (i.e. small margin between effective and toxic doses), which results in a greater likelihood of toxicity;[16,35,36] and, potentially serious adverse events (for example, seizures, arrhythmias, and coma).[16,37] Nonetheless, first-generation antidepressants could be reserved as an option on a case-by-case basis for selected patients with recurrent MDD who had previously responded to, and safely tolerated, them.

## Prescribing antidepressants for MDD

Refer to Table 1 for key considerations to guide selection of an antidepressant for MDD treatment. Table 1 provides a list of all locally-registered second-generation antidepressants with proven efficacy over placebo in achieving remission, with some variation in efficacy and tolerability (though these differences are mostly statistically insignificant).[38] Antidepressants are associated with different adverse effects, contraindications, drug interactions, and costs, which reinforces the importance of shared decision-making with the patient when selecting pharmacotherapy.

Routine use of pharmacogenomic tests to select the choice and dose of antidepressants for newly-diagnosed patients with MDD is not currently recommended due to the inconsistent and low-certainty evidence, biased by lack of blinding.[10, 39]

When initiating antidepressant therapy, **start at a low dose** to reduce the risk of adverse effects and facilitate adherence.[17] During the initial months of treatment and dose changes, monitor patients closely for emergent suicidal thoughts and behaviour, especially those under 25 years of age or with pre-existing suicide risk.[40] Advise patients to seek medical attention immediately if symptoms emerge.

Among patients with depression, observational data suggests that the risk of suicidal behaviour and self-harm may be highest during the **initial one to three months after starting an antidepressant and one month after stopping an antidepressant.**[41] Closer monitoring during these periods is therefore warranted.

### Patient communication points at new onset of MDD

Discussion regarding MDD and its treatment includes the following key points:

- Symptoms and biopsychosocial causes of MDD.
- Goal of treatment: to achieve and sustain remission, which includes relief of symptoms and restoration of functioning.[10]
- Available non-pharmacological and pharmacological treatments, and potential adverse effects.
- Pharmacological treatment course:
  - While some improvement in symptoms may occur as early as 2 weeks of starting antidepressant treatment, the full benefit is typically observed between 4 to 12 weeks.[42,43]
  - MDD management extends beyond the acute episode and includes maintenance treatment after remission, to reduce the risk of relapse.[10]
- The importance of treatment adherence: Emphasise that if the patient decides to discontinue antidepressant treatment, these medications should not be abruptly stopped but rather tapered off gradually.[18,44] This is to minimise the development of discontinuation symptoms.[17,19,§]
- Importance of returning to clinic if experiencing worsening symptoms, suicidal thoughts, abnormally elevated or irritable mood, or intolerable side effects of treatment.
- Available online resources (MindSG, Mindline), helplines to call, as well as support schemes and services.

§ Some international guidelines prefer the term ‘withdrawal symptoms’, as this reflects the potential for physical dependence to develop when antidepressants are taken for weeks to months. This ACG uses ‘discontinuation symptoms’, acknowledging its familiarity to clinicians in the local context.

**Table 1.** Key considerations for selecting a second-generation antidepressant in MDD. Antidepressants listed are locally-registered for MDD treatment. Information sourced from international literature[10,16,38,45–55] and local drug information resources[56, 57] (including package inserts). The information in this table is not exhaustive of the subject matter. Refer to package inserts and drug information resources for further details — including contraindications, drug interactions, and medication doses.

| Second-generation antidepressant for treating MDD** | Other labelled indications†† | Key precautions‡‡ | | Additional considerations<br>✚ Advantageous<br>▬ Disadvantageous<br>● May be advantageous or disadvantageous, depending on context of individual patient |
|---|---|---|---|---|
| **Selective serotonin reuptake inhibitor** | | | | |
| Escitalopram | GAD, OCD, panic disorder | Risk of bleeding abnormalities with SSRIs; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin). | Dose-dependent QTc prolongation (higher risk than other SSRIs). | ✚ Lower treatment drop-out due to side effects, compared to other antidepressants<br>● Greater propensity for weight gain compared to other antidepressants |
| Fluoxetine | Bulimia nervosa, OCD, pre-menstrual dysphoric disorder | | Strong inhibitor of CYP2D6. | ✚ Lower treatment drop-out due to side effects, compared to other antidepressants<br>✚ Suitable for patients with poor medication adherence due to a long half-life<br>✚ Lower risk of discontinuation symptoms compared to other antidepressants<br>▬ Insomnia very commonly reported<br>▬ Greater difficulty in switching to another antidepressant due to long half-life<br>● Activating effect |
| Fluvoxamine | OCD | | Strong inhibitor of CYP1A2, CYP2C19, and CYP3A4. | ● Sedating effect |
| Paroxetine | Pre-menstrual dysphoric disorder, social anxiety disorder | | Strong inhibitor of CYP2D6; contraindicated for concurrent use with CYP2D6 substrates that can prolong QT interval. | ▬ Greater propensity for anticholinergic effects compared to other antidepressants<br>▬ Higher risk of discontinuation symptoms compared to other antidepressants<br>● Greater propensity for weight gain compared to other antidepressants<br>● Sedating effect |
| Sertraline | OCD, panic disorder, pre-menstrual dysphoric disorder, PTSD, social anxiety disorder | Risk of bleeding abnormalities with SSRIs; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin). | | ✚ Dose adjustment not routinely required in renal insufficiency<br>▬ Insomnia very commonly reported<br>● Activating effect |
| **Serotonin–norepinephrine reuptake inhibitor** | | | | |
| Desvenlafaxine | Nil | Risk of bleeding abnormalities with SNRIs; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin). | May cause increased blood pressure (therefore may not be suitable for patients with uncontrolled hypertension). | ▬ Insomnia very commonly reported<br>▬ Higher risk of discontinuation symptoms compared to other antidepressants |
| Venlafaxine | GAD, panic disorder, social anxiety disorder | | | |
| Duloxetine | Diabetic peripheral neuropathic pain, GAD, pain associated with fibromyalgia | | May cause increased blood pressure and is contraindicated in patients with uncontrolled hypertension.<br>Contraindicated if substantial alcohol use is present, if severe renal impairment (creatinine clearance <30 mL/min) is present, or if liver disease is present.<br>Contraindicated for concurrent use with strong CYP1A2 inhibitors (such as ciprofloxacin and fluvoxamine). | ▬ Higher risk of discontinuation symptoms compared to other antidepressants |

*Continued on next page*

| Second-generation antidepressant for treating MDD** | Other labelled indications†† | Key precautions‡‡ | Additional considerations<br>✚ Advantageous<br>▬ Disadvantageous<br>• May be advantageous or disadvantageous, depending on context of individual patient |
|---|---|---|---|
| **Melatonergic agonist and serotonergic antagonist** | | | |
| Agomelatine | GAD | May cause hepatotoxicity; contraindicated in patients with hepatic impairment or transaminases exceeding 3x upper limit of normal.<br>Concurrent use with strong CYP1A2 inhibitors (such as ciprofloxacin and fluvoxamine) is contraindicated. | ✚ Lower treatment drop-out due to side effects, compared to other antidepressants<br>✚ Lower propensity to cause sexual dysfunction compared to SSRIs and SNRIs<br>✚ No discontinuation symptoms; no dosage tapering is needed on treatment discontinuation<br>• Sedating effect |
| **Norepinephrine and dopamine reuptake inhibitor** | | | |
| Bupropion | Nil | Contraindicated in patients with a seizure disorder or with history of/ current bulimia or anorexia nervosa.<br>Contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives. | ✚ Lower propensity to cause sexual dysfunction compared to SSRIs and SNRIs<br>✚ Evidence of efficacy for smoking cessation (off-label use)<br>▬ Insomnia very commonly reported<br>• Associated with weight loss<br>• Activating effect |
| **Noradrenergic, specific serotonergic antidepressant** | | | |
| Mirtazapine | Nil | May cause orthostatic hypotension. | ✚ Lower propensity for sexual dysfunction compared to SSRIs and SNRIs<br>✚ Lower propensity for hyponatraemia compared to SSRIs and SNRIs<br>▬ Greater propensity for anticholinergic effects compared to other antidepressants<br>• Greater propensity for weight gain compared to other antidepressants<br>• Sedating effect |
| **Serotonin antagonist and reuptake inhibitor** | | | |
| Trazodone | Nil | May cause orthostatic hypotension and QTc prolongation.<br>Risk of bleeding abnormalities; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin). | ✚ Lower risk of discontinuation symptoms compared to other antidepressants<br>▬ Higher treatment drop-out due to side effects, compared to other antidepressants<br>• Sedating effect |
| **Multimodal serotonergic antidepressant** | | | |
| Vortioxetine | Nil | Risk of bleeding abnormalities; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin). | ✚ Lower treatment drop-out due to side effects, compared to other antidepressants<br>✚ Dose adjustment not routinely required in renal and hepatic insufficiency<br>✚ Evidence of efficacy for improving cognitive function and memory (off-label use) |

CYP1A2, cytochrome P450 family 1 subfamily A member 2; CYP2C19, cytochrome P450 family 2 subfamily C member 19; CYP2D6, cytochrome P450 family 2 subfamily D member 6; CYP3A4, cytochrome P450 family 3 subfamily A member 4; GAD, generalised anxiety disorder; MDD, major depressive disorder; NSAIDs, non-steroidal anti-inflammatory drugs; OCD, obsessive–compulsive disorder; PTSD, post–traumatic stress disorder; QTc, corrected QT interval; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors

** Medications underlined denote availability on government subsidy list at the time of publication. Please refer to the Ministry of Health website for the latest list of subsidised medications.

†† Typically, an antidepressant may be used to simultaneously treat MDD and other labelled indications. However, note that such scenarios are clinically more complex - dosing and treatment strategy would need to be tailored accordingly, and may require specialist input. Labelled indications are based on available brand-specific package inserts in the Health Sciences Authority (HSA) website.

‡‡ Serotonin syndrome may occur with antidepressants, especially in cases of overdose or when an antidepressant is co-administered with other serotonergic medications (including another antidepressant). This is caused by excessive stimulation of serotonin receptors, and mild to severe symptoms may emerge (including neuromuscular abnormalities, autonomic hyperactivity, or altered mental status).[58] The risk of serotonin syndrome with agomelatine is considered to be low, as it does not increase serotonin levels.[59]

## Management considerations for special populations

### Older adults (65 years old and above)

Psychotherapy remains an effective treatment of depression for older adults.[60] The efficacy of antidepressants among this population is less established,[61] especially SSRIs.[62] Therefore, **where acceptable to the patient (i.e. receptive and able to engage in therapy) and feasible, psychotherapy is preferred** for older patients with MDD. If prescribing an antidepressant, lower doses and more gradual titration may be required due to physiological changes that accompany advancing age. Note that antidepressants (especially SSRIs and SNRIs) have been associated with hyponatraemia, although such events are overall not very common.[54] Consider also the potential for drug-drug interactions, as elderly patients may already be prescribed other medications for comorbid conditions.

### Patients with comorbid dementia

The magnitude of depression symptom reduction with psychotherapy may be small for patients with dementia,[63] although **other non-pharmacological interventions** have been found to reduce depression symptoms among this population.[64] Efficacy of antidepressants for treating depression in this cohort is not established.[65,66]

### Patients with comorbid anxiety symptoms

Comorbidity with anxiety symptoms is associated with reduced likelihood of remission in MDD,[67,68] and thus represents a higher severity of illness. **More extensive interventions** may therefore be warranted (for example, combination of an antidepressant with psychotherapy).

Evidence of antidepressant anxiolytic effects in MDD is limited but indicate that antidepressants (including SSRIs,[69] SNRIs,[70,71] bupropion,[69] and vortioxetine[72]) reduce anxiety symptoms in MDD. No significant differences between agents have been reported.[69,71] Overall, the presence of comorbid anxiety symptoms does not influence selection of antidepressant for MDD.[10] However, if patients are diagnosed with generalised anxiety disorder (GAD), note that SSRIs or SNRIs are preferred: please refer to the GAD ACG for further details.

### Patients with neurodevelopmental disorders (for example, intellectual disability, autism spectrum disorder, or attention-deficit/ hyperactivity disorder)

Patients with neurodevelopmental disorders may have atypical presentation of depression. Involve specialist care in assessment and treatment planning, as needed. Interventions should be adapted to the person's needs (for example, developmental level and communication skills).

## Patient communication points on other treatments for MDD

In addition to antidepressants and psychological treatment, various other treatments exist for MDD:

### Exercise

**Encourage exercise as a complement** to pharmacotherapy or psychological treatment for all patients with MDD, as even simple activities like walking and jogging have been found to reduce depression symptoms.[73]

### St John's Wort

Evidence suggests St. John's Wort reduces depression symptoms. However, different extract preparations were employed in RCTs,[74] limiting recommendations for St John's Wort in international guidelines.[17–19] Caution patients that St. John's Wort may interact adversely with other medications, and emphasise that **it should not be taken alongside antidepressants** due to the risk of serotonin syndrome.[75]

### Acupuncture

While recent systematic reviews have found a positive effect of acupuncture on depression symptoms, the quality of the underlying evidence remains insufficient (for example, due to risk of bias concerns in RCTs).[76,77] For patients interested in receiving acupuncture for treating MDD, **advise them not to discontinue mainstay treatment** (antidepressant and/or psychological treatment).

### Social prescribing of community-based programmes

Emerging evidence suggests that community interventions such as music therapy, art therapy, exercise programmes, and community gardening may help reduce depression symptoms. However, more research is needed to better understand their effectiveness.[78–80] For patients interested in joining community-based programmes, **advise that they may be used as a complement to mainstay treatment** (antidepressant and/or psychological treatment).

## Management of suboptimal response to initial treatment

**Recommendation 5** **If response to initial treatment is suboptimal, assess possible reasons before adjusting management strategy.**

Some improvement in symptoms may occur as early as 2 weeks after starting antidepressant treatment, although the full benefit is typically observed between 4 to 12 weeks, with adequate dosing.[42,43] Periodically monitor treatment progress in terms of symptom reduction (for example, via PHQ-9) and adverse effects of medications. Use this information to guide treatment decisions (for example, if dose or choice of antidepressant needs to be changed), as such measurement-based care enhances treatment adherence and remission rates.[81] Note that **high antidepressant doses may not be required** to elicit a treatment response. For example, the balance between SSRIs' efficacy and acceptability tends to be optimal at lower doses (fluoxetine: between 20 mg and 40 mg per day; escitalopram: between 10 mg and 20 mg per day; paroxetine: between 20 mg and 30 mg per day; sertraline: between 50 mg and 100 mg per day;[82] fluvoxamine: evidence on optimal dose is less established due to greater imprecision, but a recent systematic review suggests that its efficacy may not be increased with doses above 150 mg per day).[83]

Suboptimal response may also be observed with psychological treatment. As evidence suggests that improvement in depression symptoms may be most rapid within the first 8 to 9 sessions of psychotherapy,[84] a lack of improvement during this period may indicate the therapy is ineffective.

If treatment response remains suboptimal - for example, less than 50% reduction in depression symptom scores - after an adequate treatment trial (about **4 to 12 weeks of antidepressant at appropriate therapeutic dose** and/or about **8 to 9 sessions of psychotherapy**), assess possible reasons for this.[16] Reasons may include:[16, 18, 19, 85]

### Ongoing psychosocial stressors and poor coping mechanisms

- For example, financial pressure, interpersonal conflicts, or recent diagnosis of a severe medical condition.

### Suboptimal treatment adherence

- Routinely check compliance to treatment: patients may independently stop taking medication or reduce the dose in response to adverse effects or if they perceive treatment is ineffective.

### Diagnostic inaccuracy or presence of other mental health conditions

- For example, missed diagnosis of bipolar or psychotic depression, addictive disorder, or personality disorder.
- Note that the emergence of manic or hypomanic symptoms during antidepressant treatment may indicate the presence of bipolar depression.[5]

### Comorbid conditions that may limit response to treatment or mimic depression symptoms such as fatigue

- For example, anaemia, hypothyroidism, poor glycaemic regulation, or antidepressant-induced hyponatraemia.

If response remains suboptimal after assessing, and where possible, addressing reasons for treatment ineffectiveness, a change in management strategy may be required (please refer to Figure 4 for recommended strategies).

**Referral considerations**

Specialist involvement may be required for assessing and addressing reasons for initial treatment ineffectiveness (for example, to detect and treat comorbid psychosis).

If the second treatment attempt (Figure 4) still produces suboptimal response, patients may benefit from referral to specialist services.

**Figure 4.** Changes in management strategy when initial response is suboptimal

## ✓ Recommended adjustments to management strategy

When there is a need to adjust the management strategy, treatment with a combination of psychotherapy and antidepressants is the approach best supported by current evidence.[86] However, shared decision-making with the patient is required, as some may prefer less intensive treatment options, such as switching to another antidepressant or to another psychological treatment.

### When initial treatment involved psychological treatment

**+** Add an antidepressant if this is not currently provided

Direct evidence supporting this approach is limited,[87] though the overall efficacy of combining psychotherapy with antidepressants is well established.[26,27]

**➡** Switch to an alternative psychological treatment

This may involve switching from supportive counselling to psychotherapy, or switching from one form of psychotherapy to another. There is a lack of direct supporting evidence,[86] but this option may be useful for patients who are not willing to start antidepressants.

### When initial treatment involved an antidepressant

**+** Add psychotherapy if this is not currently provided

Evidence indicates that this combined approach results in sizeable increases to remission rates, compared to solely continuing antidepressant treatment.[86]

**+** Add *mirtazapine* to an *SSRI* or an *SNRI*

This approach also increases remission rates, although with a smaller magnitude of benefit compared to adding psychotherapy.[86]

**➡** Switch to another antidepressant

Evidence supporting this approach is limited;[86] Note that a wash-out period may be required when switching to a new medication.[19]

**➡** Switch to psychological treatment

Although there is a lack of direct evidence to support this approach,[86] it may be useful for patients unwilling to continue antidepressant treatment.

SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

## ✗ Strategies that are not preferred for treating depression, compared to the strategies above

**Not preferred as routine practice in primary care without consulting a specialist:**

- Adding an antipsychotic medication (such as aripiprazole, brexpiprazole, or quetiapine) to an antidepressant: While this may result in increased remission rates, it may also result in increased treatment discontinuation due to adverse effects.[86]

**Not preferred as evidence of efficacy is not currently established:**

- Switching from an antidepressant to an antipsychotic: this approach has not demonstrated efficacy in reducing depression symptoms and results in increased treatment discontinuation due to adverse effects.[86]
- Adding lithium or anti-epileptics (such as lamotrigine, sodium valproate, or topiramate) to an antidepressant: Current evidence examines lithium and anti-epileptics as augmentation but not as switching options. Evidence of efficacy for these augmentation agents is not established.[86]

## Management to reduce risk of relapse

**Recommendation 6**

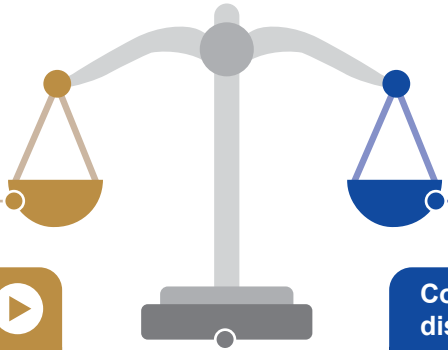
**Continue treatment after remission to reduce relapse risk; if antidepressants are prescribed, continue at optimal dose for at least 6 months after remission.**

After remission from the acute MDD episode, patients who receive no treatment are at higher risk of relapse compared to those who do.[13,14] Therefore, it is important to provide maintenance treatment post-remission. Current evidence indicates that the following treatments are effective in reducing relapse risk:[13–15]

- Continuation of antidepressant treatment.
- Provision of psychological treatment (effective even with tapering of antidepressants). Tailor the duration of psychological treatment based on individual patient's needs.
- Combination of psychological treatment and antidepressants.

Continuation of antidepressants for at least 6 months after remission is recommended because relapse occurs most frequently during this time.[14] Maintain the same dose that achieved remission in the acute phase (optimal dose),[16,19] unless there are reasons to adjust it (for example, due to adverse effects).[19] After 6 months, initiate a conversation with the patient for shared decision-making regarding further continuation of antidepressants. Consider the following key factors (Figure 5) when making a shared decision with the patient.

**Figure 5.** Key considerations for continuing or discontinuing antidepressants after 6-month maintenance treatment



**Considerations for continuing antidepressants**

- Elevated risk of relapse with discontinuation.[14]
- The presence of key factors associated with relapse risk, such as the presence of post-treatment residual symptoms, prior depression episodes, or childhood trauma.[89] For patients assessed to be at high risk of relapse, international guidelines recommend continuing antidepressants for at least two years after remission.[10,18]

**Considerations for discontinuing antidepressants**

- Relapse risk may be managed by providing psychological treatment while tapering antidepressants.[13,88]
- Greater difficulty in discontinuing antidepressants after longer duration of use, due to greater incidence of discontinuation symptoms.[48]

**Clinical uncertainty**

As few MDD antidepressant randomised controlled trials (RCTs) have follow-up periods of over 1 year, high-quality evidence on long-term benefits and harms is not yet established[14] and is still emerging.[90] Observational studies have investigated potential health harms with long-term antidepressant use and report mixed findings, but remain inconclusive due to concerns of confounding.[91,92]

If a decision is made to discontinue antidepressant treatment, minimise discontinuation symptoms by **gradually reducing (tapering) the antidepressant dose**.[17] Longer duration of antidepressant use is associated with greater incidence of discontinuation symptoms. Hence, slower tapering may be required.[48] Antidepressants with a short half-life also need to be tapered more slowly.[19]

Among patients with depression, observational data suggests that the risk of suicidal behaviour and self-harm may be highest during the initial **one to three months after starting an antidepressant and one month after stopping an antidepressant**.[41] Closer monitoring during these periods is therefore warranted.

### Patient communication points after remission

- Explain the need for maintenance treatment post-remission: to reduce the risk of relapse.[13,14]
- Discuss the options of continuing or discontinuing antidepressants after 6 months of maintenance treatment (Figure 5).
- Advise patients to monitor for discontinuation symptoms and potential increase in suicidality when antidepressants are discontinued; antidepressant discontinuation symptoms can be summarised using the acronym FINISH:[93]
  - **F**lu-like symptoms (lethargy, fatigue, headache, aches, sweating)
  - **I**nsomnia (with vivid dreams or nightmares)
  - **N**ausea (vomiting may occur)
  - **I**mbalance (dizziness, light-headedness)
  - **S**ensory disturbances (“burning” or “tingling” sensations)
  - **H**yperarousal (anxiety, irritability, agitation, aggression, mania)
- Advise patients to monitor for symptoms of relapse, so that treatment can be provided promptly.

## Supplement 1: MDD management considerations for perinatal populations

This supplement addresses the principles of care for pregnant and postpartum women. As an additional and practical resource for primary and generalist care, the principles presented here are not exhaustive of the subject matter, acknowledging that healthcare professionals in these settings may also refer or co-manage with specialists as required.

### Pregnant and postpartum women

#### Assessment

- The Edinburgh Postnatal Depression Scale is a tailored assessment tool and may be used to assess depression symptoms in the pregnant or postpartum stage.[94]
- DSM or ICD criteria informs the diagnosis of MDD. Note that sleep, energy levels, and appetite may be disrupted during pregnancy, which may be conflated with MDD symptoms.
- In addition to typical mental state assessments for adults, check for any impairments to mother-child bonding. Other factors that inform management planning include obstetric health, breastfeeding status, experience of pregnancy/parenting (including specific stressors), social or partner support, and caregiving responsibilities.[94] Problems with sleep can be addressed, if present.[95]

#### Principles of management for patients with a diagnosis of MDD (if managing in primary or generalist care)

- Overall, psychological treatment is preferred over antidepressants for treating MDD in the perinatal period:[16,96–98]
  - Patients in these populations tend to prefer non-pharmacological treatment.[16,99]
  - Psychotherapy has proven efficacy for treating perinatal depression, especially cognitive behavioural therapy.[100,101] Current evidence indicates that supportive counselling is efficacious in treating postpartum depression.[101]
- For patients at higher severity, optimise decision-making by discussing treatment options, including medications and seeking specialist advice or referral.
- Given that poor mental health is a significant contributor to maternal mortality[102] and that perinatal depression may also result in adverse health outcomes for the child,[103,104] providing antidepressant treatment is preferred over not treating perinatal depression:

Considerations for use of antidepressants in perinatal MDD

| | Benefits | | Risks |
|---|---|---|---|
| Pregnancy | No direct evidence of efficacy,[105] although efficacy among the general adult population is well established.[38] | For women already receiving antidepressant treatment, discontinuation during pregnancy may be associated with increased risk of relapse.[106] | There is considerable uncertainty in the evidence concerning adverse outcomes with antidepressant use during pregnancy, and these adverse outcomes remain overall rare: potential risks include those to the mother (such as postpartum haemorrhage and preeclampsia) and to the child (including risk of pre-term birth and lower APGAR scores).[105,107,108] |
| Postpartum | Evidence of efficacy, though few trials have been conducted.[109] Nonetheless, efficacy among the general adult population is well established.[38] | | Uncertain as evidence on risks is limited.[109,110] |

  - If starting an antidepressant, note that international guidelines recommend SSRIs,[18,96,111,§§] although evidence of efficacy is only established for sertraline in treating postpartum depression.[105] Most reports have found no adverse effects of sertraline on breastfed infants.[112]
  - Whilst not developed specifically for the local population, references such as UKTIS, MotherToBaby, and LactMed may facilitate patient education and discussion.
  - Always check if the patient is breastfeeding so that lactational safety of medications can be taken into account.
  - Consider specialist input if deciding to initiate an antidepressant.

#### Clinical and community resources

Non-pharmacological and pharmacological interventions tailored for the perinatal population are available in tertiary care settings, such as:

- The National University Hospital Women's Emotional Health Service
- KK Women's and Children's Hospital
- Institute of Mental Health

APGAR, appearance, pulse, grimace, activity, respiration; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; MDD, major depressive disorder; SSRIs, selective serotonin reuptake inhibitors; UKTIS, UK Teratology Information Service

§§ Please refer to package inserts for brand-specific indications and guidance on use in perinatal populations.

In addition to the Expert Group, the following perinatal psychiatry expert advisers generously contributed their insights and reviewed this supplement:
Asst Prof Cornelia Chee (NUH) | Clin Assoc Prof Helen Chen (KKH) | Dr Gillian Lim (IMH)

## Supplement 2: MDD management considerations for children and adolescents

This supplement addresses the principles of care for children and adolescents. As an additional and practical resource for primary and generalist care, the principles presented here are not exhaustive of the subject matter, acknowledging that healthcare professionals in these settings can consult child and adolescent mental health service providers and may also refer or co-manage with specialists as required.

### Children (6 to 12 years old) and adolescents (13 to 17 years old)

#### Assessment

- A comprehensive assessment and holistic understanding of the patient's profile is important for case formulation:
  - This includes social, family, and educational context; developmental level, communication needs, and any learning disability; comorbidities; changes from the premorbid state in terms of mood and functioning; as well as any mental health problems faced by parents/ caregivers/ other family members.
  - Corroborative history-taking, incorporating inputs from parents/ guardians and schools, is especially important for children as they may not be able to adequately express their emotional state or symptoms. Such inputs may also aid in determining if presenting symptoms are due to depression or developmental delays.
  - For adolescents, the HEEADSSS framework may be helpful to progressively discuss the patient's psychosocial context and direct management.[113]
  - Sufficient time should be allocated for assessments.
- DSM or ICD criteria informs the diagnosis of MDD.[4,5] Note that depression may present differently in children and adolescents, compared to adults: for example, undue irritability may be observed instead of a sad mood. Separation anxiety may accompany MDD in children.[5]

#### Principles of management for patients with a diagnosis of MDD (if managing in primary or generalist care)

- Overall, efficacy of psychological treatment is better supported by current evidence compared to antidepressants for children and adolescents.[114–116] Given also the risk of adverse effects with antidepressants,[116] **psychological treatment is preferred as the first treatment option**.[117]
  - Supportive counselling or psychotherapy are efficacious treatments for children and adolescent depression;[114] family-based therapy may be useful as an adjunct treatment.[118]
- For adolescents who do not respond to psychological treatment or have more severe symptoms, addition of fluoxetine*** may help reduce depression symptoms[119] and increase functioning.[120]
  - While evidence indicates that escitalopram is also efficacious in treating depression in adolescents,[119,120] note that this currently constitutes off-label use as local package inserts do not recommend its use in patients under 18 years old.†††
  - Evidence regarding the use of other antidepressants for MDD treatment in adolescents is not yet well established.[116,119]
  - Consider specialist input if deciding to initiate an antidepressant.
  - Close monitoring for emergent suicidal thoughts and behaviour, especially during the period of treatment initiation, forms part of ongoing patient assessment.[117]
- Evidence regarding the use of antidepressants for children with MDD is not yet well established.[119,120]

#### Clinical and community resources

- School-based counselling services can provide access to multidisciplinary REACH teams. IMH, KKH, and NUH REACH teams provide mental health assessment, holistic case management, and therapy services.
- Youth Integrated Teams in the community offer assessment and non-pharmacological treatment options.
- IMH's CHAT service provides mental health assessments and supportive help for young persons aged 16–30 years old. Youth Community Outreach Teams are also available islandwide for screening and linking up to relevant services.

CHAT, Centre of Excellence for Youth Mental Health; DSM, Diagnostic and Statistical Manual of Mental Disorders; HEEADSSS, Home, Education/Employment, Eating, Activities, Drugs, Sexuality, Suicidal ideation and Safety; IMH, Institute of Mental Health; ICD, International Classification of Diseases; KKH, KK Women's and Children's Hospital; MDD, major depressive disorder; NUH, National University Hospital; REACH, Response, Early intervention and Assessment in Community mental Health

*** Local package inserts do not recommend use of fluoxetine in children (age range not specified).

††† The US Food and Drug Administration (FDA) has approved escitalopram for treating MDD in patients 12 years old and above.

In addition to the Expert Group, the following child and adolescent psychiatry expert advisers generously contributed their insights and reviewed this supplement: Dr Lim Choon Guan (IMH) | Clin Asst Prof Vicknesan Jeyan Marimuttu (KKH) | Asst Prof Celine Wong (NUH)

## References

**Click or scan the QR code for the reference list to this clinical guideline**

## Evidence-to-Recommendation Framework

**Click or scan the QR code to view the Evidence-to-Recommendation Framework for the recommendations in this clinical guideline**

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## About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare by conducting health technology assessments (HTA), publishing healthcare guidance and providing education. ACE develops ACE Clinical Guidelines (ACGs) to inform specific areas of clinical practice. ACGs are usually reviewed around five years after publication, or earlier, if new evidence emerges that requires substantive changes to the recommendations. To access this ACG online, along with other ACGs published to date, please visit www.ace-hta.gov.sg/acg

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