ACE CLINICAL GUIDANCE

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Generalised anxiety disorder

Easing burden and enabling remission

Objective	Scope	Target audience
To support management of generalised anxiety disorder (GAD), for achieving remission and reducing relapse	Non-pharmacological and pharmacological management of GAD in adults	This clinical guidance is relevant to all healthcare professionals caring for patients with diagnosed GAD, especially those in primary or generalist care

Generalised anxiety disorder (GAD) is characterised by excessive anxiety and worry across multiple domains of life, with additional physical and/or cognitive symptoms, that lead to significant distress and functional impairment. GAD is reported by patients to have the most significant impact on quality of life compared to other mental health disorders studied in Singapore.[1]

Enhancing the capacity of community-based mental health care through a tiered care model is a focus area of the 2023 National Mental Health and Well-being Strategy. Accordingly, this ACE Clinical Guidance (ACG) aims to inform the clinical management of adults (18 years old and above) in primary and generalist care with a diagnosis of GAD, including those with comorbid depression or other anxiety disorders. Guidance on major depressive disorder (MDD) can be found in the ACG *Major depressive disorder – achieving and sustaining remission*.

Statement of Intent

This ACE Clinical Guidance (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.

ACE agency for care effectiveness

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Chapter of General Physicians, CPS
College of Obstetricians & Gynaecologists, Singapore
College of Psychiatrists

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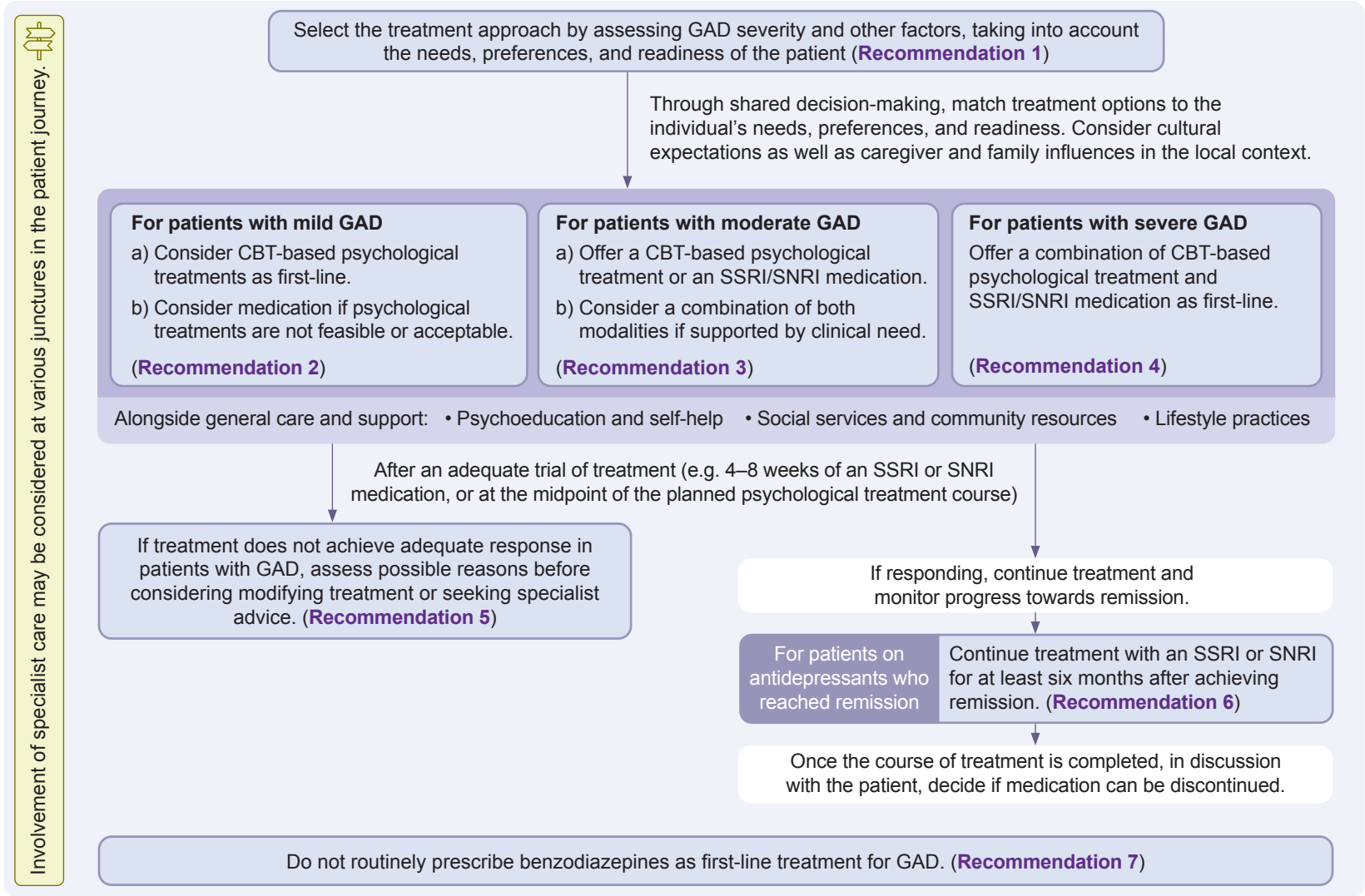
Figure 1. Overview of GAD management

The management goals for GAD include promoting remission and reducing the risk of relapse.

- The clinical course of GAD varies. For some individuals, it may be episodic, while for others it is persistent and chronic.[2,3]
- To effectively tailor management goals, it is important to understand the patient's views on how the condition affects their daily life, and to envision what would improvement and living well be like for them.

For details on diagnostic assessment of GAD, clinicians may refer to the latest Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases.



CBT: cognitive behavioural therapy; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin–noradrenaline reuptake inhibitor

Assessment to guide management

Recommendation 1 **Select the treatment approach by assessing GAD severity and other factors, taking into account the needs, preferences, and readiness of the patient.**

Assessing the severity of symptoms, degree of functional impairment, and other patient factors informs treatment planning.

GAD severity

Clinicians should assess whether a patient's condition is mild, moderate, or severe, based on the intensity of symptoms and the impact on subjective distress and daily functioning.

- The Generalised Anxiety Disorder 7-item (GAD-7) scale can be used to monitor the intensity of GAD symptoms over time.[4]
- Functioning can be assessed through the additional functional question in GAD-7 or more systematically through rating scales such as the World Health Organization Disability Assessment Schedule 2.0. Apart from the overall level of disability, clinicians can take note of specific domains where the patient experiences significant difficulties due to their mental health condition.

Determine severity of GAD

The GAD-7 scale can be used to provide an initial, brief assessment of intensity or frequency of symptoms. Scores are grouped into increasing severity levels, using 5, 10, and 15 as cutoffs:

• 5–9 points	• 10–14 points	• 15–21 points

Also consider difficulties in daily activities (e.g. work, education, household), self-care, social interactions, and participation in community, compared to the patient's premorbid state.

In some cases, the degree of functional impairment may be marked and more severe than the GAD-7 score suggests, which may influence the treatment approach (including consideration of a higher tier of care), prompt further evaluation of the source of impairment, or both.

Manage as

Mild GAD	Moderate GAD	Severe GAD

Other patient factors

Overlay other patient factors to tailor treatment approach to the individual. Patient factors are explored in more detail below and continues on the following page.

Overlay other patient factors

Patient needs, preferences, and readiness

Consider patient needs, preferences, and readiness by discussing and agreeing on:[5,6]

- Goals of treatment
- Preference between treatment modalities
- Willingness and ability to engage in psychological treatment
- Ability to adhere to regular medication

Comorbid mental health conditions

- First-line treatment options for GAD overlap with MDD and other anxiety disorders. See *Management considerations for comorbid MDD or anxiety disorders* (page 9) for additional considerations.
- Consider involving specialist care for patients with other mental health conditions such as comorbid personality disorders, eating disorders, substance use disorder, schizophrenia, or bipolar disorder.

Comorbid physical illnesses

- If pharmacological treatment is chosen, select medications with proven safety in comorbid physical illnesses and less potential for drug-drug interactions.
- Adjust dose for renal and hepatic impairment, if appropriate.

Social and environmental factors

Identify adverse life events, relationship conflicts, and stressors at home, workplace, or school. Some stressors can be addressed through social care and assistance.[7]

Substance use

Specialised, integrated treatment may be suitable to address both substance use (e.g. alcohol, nicotine, prescription medications, or illicit drugs) and GAD.

GAD treatment history and past episodes

Use past responses to medication or psychological treatment to help guide choice of treatment.

Elderly

- Due to age-related changes, disability, and medical comorbidities, the balance of benefits and risks of GAD treatments in older adults should be assessed individually.
- Though more research is needed on a wide range of psychological treatments, a CBT-based approach has been shown to be effective.[8] Modifications for different cognitive and learning abilities may be needed.[9,10]
- If prescribing medication, start at low doses and monitor closely due to higher sensitivity to adverse effects.

Perinatal

See Supplement 3 (page 16) for principles of care for pregnant and postpartum women.

Neurodevelopmental disorders (e.g. intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder)

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

Consider specialist involvement

Risk of harm to self and others

Risk of harm to self

GAD is associated with an increased risk of having suicidal thoughts, planning, and attempts.[11]

Use an empathetic patient-centred approach to identify any thoughts of suicide and planning, as discussions often carry stigma.[12]

Clinical judgment is essential, and can be informed by questions developed to assess risk. An example is the Columbia-Suicide Severity Rating Scale (C-SSRS) screener. In devising a safety plan, it is also important to understand the patient's risk factors (e.g. past self-harm, hopelessness), and protective factors (e.g. social support).

Risk of harm to others

Assess if the patient has any thoughts or plans to harm others.

- Refer to the upcoming *Practice Guide for Tiered Care Model for Mental Health (Adult)* for further details on suicide risk management and red flag situations. Patients at high risk may require immediate medical attention at emergency services.
- Over the GAD treatment course, the safety plan may need to be revisited.
- Monitor closely for emergent suicidal thoughts and behaviour when initiating any antidepressant medication.
- Collaborate with other providers or family/caregivers to ensure support is in place.

Consider specialist involvement

Treatment

Treatment for GAD is broadly categorised into psychological, pharmacological, or a combination of both modalities.

General care and support complement pharmacological or psychological treatments.

General care and support

Psychoeducation and self-help

- Provide psychoeducation to all patients (and caregivers if applicable) on the disorder, treatment options, potential benefits and adverse effects, and support channels.
- Provide access to self-help materials, such as through Mind SG and Mindline.sg, and helplines.

Social services and community resources

- Refer to social services for financial assistance, social support, unemployment support, housing issues, and other stressors, depending on need.
- Patients and caregivers may also be able to find support schemes and services through SupportGoWhere.
- Connect patients with support groups and peer support specialists.

Lifestyle practices

- Advise structured physical exercise (e.g. aerobic or resistance training or both) for patients not meeting national physical activity guidelines.[13]
- Suggest mind-body practices (e.g. yoga, taichi).[14–16]
- Suggest stress management techniques.[17]
- Advise reducing caffeine intake.[18]
- Promote good sleep hygiene.

Psychological treatment

Cognitive behavioural therapy (CBT) has the most empirical support for GAD.[19–21] Apart from traditional CBT, other approaches include third-wave CBT (e.g. acceptance and commitment therapy, mindfulness-based cognitive therapy) and transdiagnostic approaches (treatments that target shared features across several disorders).[22]

Psychological treatments

Common elements of CBT-based approaches are psychoeducation, cognitive restructuring, behavioural techniques, relaxation, stress and worry management, problem-solving, and relapse prevention. Sleep management may be relevant if sleep is a concern. The number of sessions can vary depending on the patient's progress and needs.

Delivery format

Face-to-face therapy has the strongest evidence base for GAD. Guided internet-delivered therapy is emerging as an alternative for suitable individuals with mild to moderate conditions, who may prefer the flexibility and accessibility of learning via online materials supported by trained professionals.

Applied relaxation, a non-CBT-based approach that teaches patients to counter anxiety with relaxation practices, also has some evidence of efficacy for GAD.[19]

Pharmacological treatment

Though commonly referred to as 'antidepressants', **selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs) have anxiolytic effects, and are established first-line medications for GAD.**[23,24] The choice between individual SSRIs and SNRIs can be guided by factors like the patient's medical history, concomitant medications, risk of serious adverse effects, and hepatic or renal impairment (see Supplement 1).

SSRI and SNRI medications

- SSRI and SNRI medications take time to work, and in some cases may aggravate anxiety symptoms in the initial few weeks. An adequate trial typically requires 4–8 weeks of treatment,[25] though response may take longer for some patients. Start at a low dose to minimise the initial increase in anxiety.
- Common adverse effects include changes in appetite and weight, restlessness, abnormal dreams, nausea and vomiting, dizziness, sexual dysfunction, and sleep disturbances.[26] SNRIs may also increase blood pressure and heart rate.
- During the initial months of treatment and dose changes, monitor all patients closely for emergent suicidal thoughts and behaviour, especially those under 25 years of age or with pre-existing suicide risk.[27] Advise patients to seek medical attention immediately if symptoms emerge.
- Medication information leaflets are available in plain language for patients on HealthHub.

If SSRIs and SNRIs are not suitable or poorly tolerated, effective alternatives include agomelatine, mirtazapine (off-label use), and pregabalin.[23] Note that agomelatine carries a risk of liver injury (requiring regular monitoring of liver function) and mirtazapine may cause sedation and weight gain. Consider seeking specialist input for cases where pregabalin might be useful.

Other anxiolytic medications mentioned in this guidance

- Hydroxyzine may be useful in mild GAD (see Recommendation 2) or as an adjunct.[28] It carries a risk of anticholinergic effects and excessive sleepiness, and may prolong QTc interval.
- Some benzodiazepines may be used short-term for anxiety symptoms (see Recommendation 7).

A note on use of complementary and alternative medicine

- While there is emerging trial data with lavender oil and ashwagandha extracts, more evidence is required to establish efficacy and long-term safety. Varying product quality and lack of standardisation are additional limitations.[29]
- Consider checking for use when taking medication history, to pre-empt herb-drug interactions (e.g. St John's Wort increase the risk of serotonin syndrome when taken with SSRIs).[29]

Recommendation 2

For patients with mild GAD:

a) Consider CBT-based psychological treatments as first-line.

b) Consider medication if psychological treatments are not feasible or acceptable.

CBT-based psychological treatments are preferred when GAD severity is mild, as they are associated with fewer adverse effects compared to pharmacotherapy. However, they may not be feasible or acceptable, such as when:

- 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 (e.g. due to cognitive impairment).

Medication options for mild GAD are either an SSRI or SNRI medication or a trial of hydroxyzine (with a plan to start CBT-based psychological treatment or SSRI or SNRI, if ineffective).

Hydroxyzine has limited usefulness for comorbid depression symptoms, where proven treatments such as psychological therapy or SSRI/SNRI medications are preferred. Due to significant anticholinergic effects, hydroxyzine is also less suitable for elderly patients.

Consider specialist involvement

Recommendation 3

For patients with moderate GAD:
a) Offer a CBT-based psychological treatment or an SSRI/SNRI medication.
b) Consider a combination of both modalities if supported by clinical need.

As either psychological treatment or an SSRI or SNRI medication can be offered first-line for moderate GAD,[19–21,23,24] various factors unique to each patient's situation, including personal preferences and values, must be considered when determining the most appropriate treatment option. Features of each treatment modality are described in Table 1:

Table 1. Features of psychological treatment and SSRI or SNRI medication

Psychological treatment		SSRI or SNRI medication
Typically held weekly or fortnightly, with the total number tailored to each patient's needs.	**Duration and frequency**	Daily administration for at least 4–8 weeks, with continuation for at least another 6 months from remission if responding well.
Not well-documented; examples are unpleasant feelings and memories.[30]	**Adverse effects**	Range from common to rare adverse effects; dependent on medication class (see *SSRI and SNRI medications* on page 7)
Not applicable.	**Interaction with other treatment or medical condition**	Some drug-drug or disease-drug interactions can be clinically significant.
Possible, dependent on the professional's expertise.	**Ability to treat comorbid MDD and other anxiety disorders**	Possible for SSRI and SNRI medications to be effective.

It is unclear from available evidence if combined treatment is more effective than single treatment modality alone. Circumstances that favour combination treatment, based on clinical experience, include:

- Presence of comorbid MDD, panic disorder, or social anxiety disorder
- Previous treatment response
- Intense or prolonged psychosocial stressors
- Poor social support
- Marked functional impairment

Recommendation 4

For patients with severe GAD, offer a combination of CBT-based psychological treatment and SSRI/SNRI medication as first-line.

Research on combination treatment approaches for GAD is limited.[31,32] The potential benefits need to be weighed against higher treatment burden, to ensure patients can adhere to treatment.

When combination treatment is not feasible or acceptable, either CBT-based psychological treatment or SSRI or SNRI medication can be offered as alternatives.

Psychiatrist-led services with the ability to treat more complex cases are preferred for severe GAD due to possible comorbidities and severity of the condition. Depending on the setting, co-management with specialists may be feasible.

Additional remarks: The recommendation strength is based predominantly on expert consensus. Please click here for the full rationale.

Consider specialist involvement

Management considerations for comorbid MDD or anxiety disorders

- The presence of comorbid MDD and other anxiety disorders contribute to overall functional impairment and may reduce treatment response and remission.[33,34]
- As for GAD, SSRI and SNRI medications are shown to be effective for comorbid depression and other anxiety disorders like panic disorder and social anxiety disorder.[35,36]
- Psychological treatment can be tailored to address multiple diagnoses.[37]
  - CBT techniques specific to panic disorder (PD) and social anxiety disorder (SAD) may be required.
  - Specific phobias differ from other anxiety disorders in that they are mainly treated with behavioural treatment (exposure).
- When GAD coexists with MDD, PD, or SAD, a combination of psychological treatment and pharmacotherapy can be considered.[38–40]

Management of suboptimal response to initial treatment

Recommendation 5

If treatment does not achieve adequate response in patients with GAD, assess possible reasons before considering modifying treatment or seeking specialist advice.

Assess response, evaluate patient adherence, and monitor for any adverse effects throughout treatment with psychological treatments and/or medication. It's important to note the absence of a single definition for response in GAD.

For SSRI and SNRI medications, the time needed to find an optimal dose differs for each patient. As a general guide, the full benefit of an antidepressant should be assessed after 4–8 weeks of treatment, including any titration to reach the recommended dose or range if suitable.[a]

For psychological treatment, the number of preparatory sessions required to understand therapy work can vary; response could be evaluated at the midpoint of the planned treatment course.

Assessing response

Response can be evaluated by whether patients have experienced significant improvement in symptoms and functioning, compared against their management goal(s), incorporating both clinical judgement and the patient's perspective.

To inform clinical judgment, some clinicians may find it helpful to have a practical guide on when treatment is likely ineffective after an adequate trial at an optimal dose. For example, a Clinical Global Impressions-Improvement score >2 or <20% improvement on the GAD-7 scale can inform judgment that response could be inadequate.[41,42] However, the patient's perspective remains important in determining the significance of change.

When an inadequate response is observed (after an adequate trial of treatment), possible reasons that can be evaluated and addressed include:[43]

- Ongoing psychosocial stressors
- Suboptimal treatment adherence
- Misdiagnosis or presence of other mental health conditions
- Comorbid conditions with symptoms that may mimic those of GAD, e.g. hyperthyroidism, arrhythmia

a. Optimal therapeutic doses are not well-established in GAD. Consider adjusting dose based on early response and tolerability, as well as patient profile.

Modifying treatment

If the above reasons do not fully explain the response, consider modifying treatment. The following treatment approaches may be considered (in no particular order) if initial treatment is ineffective (Table 2). As limited evidence is available to inform optimal sequencing of treatment in GAD, **choose next-step treatment based on individual patient characteristics and shared decision-making**. Seek specialist involvement if response remains inadequate after two trials of treatment, or earlier if needed (e.g. worsening or new symptoms, clinical need for another treatment, tolerability issues with antidepressants).

Table 2. Changes in management strategy when response to an adequate trial of treatment is suboptimal

Inadequate response to psychological treatment

Possible strategies	Considerations
▶ Add an SSRI or SNRI medication to psychological treatment	May be considered to augment response to psychological treatment, especially if there was some improvement on initial treatment.
▶ Refer to psychological services based in hospital outpatient settings	May be considered for patients who prefer non-pharmacological treatment, and who can benefit from higher intensity of psychological treatment.
▶ Stop psychological treatment and start an SSRI or SNRI medication	May be considered if there was none or very minimal response to psychological treatment, or if patient is unwilling to continue with psychological treatment.

Inadequate response to an SSRI or SNRI medication

Possible strategies	Considerations
▶ Change to another antidepressant: SSRI, SNRI, or other second-generation antidepressant with proven efficacy for GAD	Switching from one antidepressant to another must be done with careful monitoring. The switching strategy varies depending on the medication (see Supplement 2 for switching between SSRIs and SNRIs).
▶ Add CBT-based psychological treatment to antidepressant medication[44,45]	May be considered to augment response to medication, especially if there was some improvement on initial treatment.
▶ Taper medication and start CBT-based psychological treatment	May be considered if patient is unwilling to continue with pharmacological treatment. Taper antidepressant medication to prevent discontinuation symptoms.

For inadequate response following initial combination treatment, the same review process (as described on the previous page) can take place, to ensure that possible reasons are addressed. If the response cannot be explained, consider seeking specialist advice as this can be a sign of complex mental health need.

Consider specialist involvement

Management to reduce risk of relapse

Recommendation 6 **Continue treatment with an SSRI or SNRI for at least six months after achieving remission.**

For patients who reach remission on SSRI or SNRI treatment, continuation of the same dose for at least another 6 months (up to 12 months) has been shown to lead to lower relapse rates.[46] It is important to note the absence of a single definition for remission in GAD. A guide for assessing these outcomes is provided below.

Assessing remission

Remission in GAD can be evaluated by all of the following:

- Significant improvement in symptoms from baseline
- No longer meeting diagnostic criteria, with minimal symptoms
- Restoration of premorbid functioning and improved quality of life

On an individual basis, clinicians may also judge remission by other personalised management goal(s) agreed on with the patient.

Consider tailoring strategies to stay well based on the individual's needs, e.g. psychoeducation on symptoms of relapse, information on where to seek help, self-help resources, engagement of social support networks, lifestyle and wellness programmes, and regular follow-up.

Role of psychological treatment in preventing relapse

After remission is reached on medication, the evidence for alternative options such as changing to or adding psychological treatment is limited. In those with MDD, psychological treatments or combination with maintenance antidepressants were shown to reduce the risk of relapse (of depression).[47]

Considerations for continuing or discontinuing antidepressants after 6-month maintenance treatment

Once the course of treatment is completed, in discussion with the patient, decide if medication can be discontinued, taking into account individual factors such as:

- History of relapse(s)
- Adverse effects
- Any ongoing or anticipated psychosocial stressors
- Comorbid mental health conditions
- Degree of social support, including family
- Patient preference

Gradually reduce the dose of antidepressant medications to minimise discontinuation symptoms[b] and risk of relapse. Patients can be made aware that discontinuation is often associated with distinctive symptoms (e.g. electric sensations, dizziness, depersonalisation), which usually occurs within hours or days of reducing doses or stopping the medication.[48]

b. 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.

Use of benzodiazepines in primary and generalist care

Recommendation 7 **Do not routinely prescribe benzodiazepines as first-line treatment for GAD.**

While the onset of action is faster compared to SSRIs or SNRIs,[49] prescribing benzodiazepines requires careful clinical assessment and judgment to weigh the benefits and risks for each patient. Due to the potential for dependence and tolerance, this can lead to problems like misuse and addiction, and serious withdrawal symptoms.[50,51]

Short-term use of benzodiazepines can be considered in GAD management within primary and generalist care for severe acute anxiety. Their role in treatment-resistant GAD is beyond this ACG's scope.

There are limited studies supporting use of benzodiazepines as an adjunct for increased anxiety during the initial weeks of antidepressant therapy. Alternative options should be considered first, such as initiating the antidepressant at a low dose, non-pharmacological interventions, and/or hydroxyzine. In some patients, despite alternative strategies, short-term benzodiazepine use can be considered for distressing symptoms if required.

Benzodiazepines with anxiolytic action include alprazolam, bromazepam, diazepam, and lorazepam.

Principles of prescribing benzodiazepines[c]

Assess the patient for history of substance abuse, current use of opioid medications and alcohol (or other central nervous system depressants), and presence of respiratory disease. Clinicians should consider the risk of daytime sedation and cognitive impairment, particularly in the elderly.

If prescribed, use the lowest effective dose for the shortest duration of time. Aim for short-term use (up to 2–4 weeks) and as-needed dosing.[51] Educate the patient on proper use and review for signs of problems due to dependence or tolerance. Consider specialist assessment if there is inadequate relief from short-term use, or difficulties in reducing or stopping benzodiazepine use.

Patient communication points on benzodiazepines in GAD

- Inform the dose, frequency, duration of use, and indication to manage symptoms temporarily.
- Advise on the adverse effects of the prescribed medication and its potential for tolerance, dependence, and addiction. Explain that treatment should be at the lowest effective dose for the shortest duration of time.
- Inform that the medication should not be taken with alcohol and other medications that are known to depress the central nervous system (e.g. opioids, hypnotics).

c. The ACG should be read alongside regulatory guidance on prescribing, documentation, and referral to a specialist, such as the *Licence Conditions for Outpatient Medical Service Licensees: Prescribing and Supplying Benzodiazepines and Other Hypnotics.*

 Consider specialist involvement

Supplement 1: A guide to SSRI and SNRI selection for GAD

The choice between individual SSRIs and SNRIs can be guided by factors like the patient's medical history, concomitant medications, risk of serious adverse effects, and hepatic or renal impairment.

Information is referenced from local product inserts and literature available at the time of guideline development or consolidated product monographs; refer to product inserts for full details on prescribing. Clinical judgement should be exercised at all times when making decisions for an individual patient.

Patient characteristic	Considerations	
GAD with insomnia as a symptom	Paroxetine* and fluvoxamine† are the more sedating SSRIs.[52,53]	
Hepatic disease	• SSRI: For most SSRIs, adjust dose. • SNRI: Adjust dose for venlafaxine. Duloxetine is contraindicated in pre-existing liver disease.	
Renal impairment‡	• SSRI: For most SSRIs, adjust dose. Sertraline* does not require dose adjustment. • SNRI: No dose adjustment needed for duloxetine in mild to moderate renal impairment, but it is contraindicated in severe renal impairment (creatinine clearance <30 mL/min). Adjust dose for venlafaxine.	
Elderly	• Adjust doses for the elderly, where applicable. • Consider choosing a medication with less anticholinergic activity (e.g. most SSRIs except paroxetine) and less sedation (escitalopram, sertraline, duloxetine, venlafaxine). • Fluoxetine* has a long elimination half-life and may require dose adjustment to reduce the risk of accumulation. Both SSRIs and SNRIs increase the risk of hyponatraemia and are associated with bone loss and fractures.	
Patients with hypertension	• SSRIs may be preferred as they do not affect blood pressure. • In uncontrolled hypertension, SNRIs should be avoided.	
Patients with cardiovascular disease	Sertraline* has been used safely after myocardial infarction and in heart failure.[53,54]	
Patient with neuropathic pain	Duloxetine is also indicated for neuropathic pain.	
Patients with risk factors for QTc interval prolongation (e.g. use of antiarrhythmic drugs, hypokalaemia)[55]	Escitalopram has been associated with clinically significant QTc interval prolongation.[56] Cases have also been reported for other SSRIs and venlafaxine, though it is recognised that these medications do not result in clinically significant QTc prolongation on their own.	
Patients on other medication(s) Check clinical significance of drug interactions using the patient's complete medication list. The examples shown are not exhaustive.	Medications metabolised extensively by CYP450 enzymes 1A2, 2C19, 2D6, and 3A4	Sertraline*, escitalopram, and venlafaxine, are less likely to cause CYP450-related drug interactions, as weak inhibitors.
	Diuretic medications	Monitor due to increased risk of hyponatraemia (class effect) – no preferred SSRI or SNRI
	Monoamine oxidase inhibitor (MAOI, e.g. selegiline, moclobemide, linezolid)	MAOIs should not be used concurrently with SSRIs or SNRIs due to increased risk of serotonin syndrome[57] (class effect). SSRI or SNRI treatment should only be started 2 weeks after discontinuing MAOI.
	Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants	Monitor due to increased risk of bleeding, especially upper gastrointestinal bleeding (class effect) – no preferred SSRI or SNRI

* Off-label use for GAD; efficacy based on published meta-analysis of randomised clinical trials.[23]

† Off-label use for GAD; limited RCT evidence for fluvoxamine in GAD

‡ For the purpose of dosing, renal impairment is staged using creatine clearance for most SSRI and SNRI medications. Some may use glomerular filtration rates instead.

Refer to MDD ACE Cinical Guidance, Table 1, for further information on precautions and additional considerations for selecting among SSRIs and SNRIs (except desvenlafaxine). Information on agomelatine and mirtazapine is also available.

Supplement 2: Switching between SSRI and SNRI medications

The choice of switching strategy is influenced by the following:

- Reason for switch (e.g. unable to tolerate adverse effects, inadequate response)
- Characteristics of the medications involved (e.g. half-lives, risk of discontinuation symptoms, potential for drug-drug interactions, dose and duration of current treatment)
- Patient factors (e.g. sensitivity to adverse effects, risk of relapse, ability to understand and administer medication schedule, experience of previous switches)

Patients should be provided with clear instructions and monitored closely when switching between medications. The following is a brief guide only; specialist advice or management can be sought at any point.

Switching from fluoxetine[53,58,59]

To another SSRI (escitalopram, sertraline, fluvoxamine, paroxetine)	Stop fluoxetine or consider tapering gradually to 20mg (if dose ≥40mg daily) before stopping → Washout for 4–7 days → Then start new SSRI at low dose 
To an SNRI (duloxetine, venlafaxine)	Stop fluoxetine or consider tapering gradually to 20mg (if dose ≥40mg daily) before stopping → Washout for 4–7 days → Then start SNRI at low dose  ⚠ Fluoxetine may increase exposure to duloxetine and venlafaxine as it is a strong CYP2D6 inhibitor.

Additional notes:

- Fluoxetine and its active metabolite have a long elimination half-life (4–16 days). The risk of drug-drug interactions may persist for several weeks after stopping fluoxetine.
- The duration of washout period can be individualised, based on clinical judgment.
- Other approaches (e.g. direct switch or cross-tapering) may be suitable on a case-by-case basis – seek specialist advice, if needed.[60,61]

Switching from other SSRIs (excluding fluoxetine)[53,58,59]

To another SSRI (escitalopram, sertraline, fluvoxamine, paroxetine, fluoxetine)	**Option 1:** Direct switch to the new SSRI on the next day (consider usual dose; tailor based on individual factors) 	**Option 2:** Taper then start low dose of new SSRI 	Under this option, cross-tapering may be suitable. 
To an SNRI (duloxetine, venlafaxine)	**Option 1:** Direct switch to the SNRI on the next day (consider usual dose; tailor based on individual factors) 	**Option 2:** Taper then start low dose of SNRI 	Under this option, cross-tapering cautiously may be suitable for SSRIs that do not interact with SNRIs. 
		⚠ Paroxetine may increase exposure to duloxetine and venlafaxine as a strong CYP2D6 inhibitor. ⚠ Fluvoxamine may increase exposure to duloxetine as a strong CYP1A2 inhibitor.	

Additional notes:

- Option 1: While a similar mechanism of action may lessen discontinuation symptoms, patients who have taken an antidepressant for at least 6 weeks remain at risk of such effects. Alternative approaches that involve tapering can be considered.
- Option 2 is a more conservative strategy with the lowest risk of drug-drug interactions and additive adverse effects.
- Cross-tapering:
  - Entails gradually reducing the first medication while titrating up the new one from low dose, including a period in which both medications are taken.
  - Suitable patients are those able to manage complex medication regimen or have support from competent caregivers.

Switching from SNRIs[53,58,62]

To an SSRI (escitalopram, sertraline, fluvoxamine, paroxetine, fluoxetine)	**Option 1:** Direct switch to the SSRI on the next day (consider usual dose; tailor based on individual factors) 	**Option 2:** Taper then start low dose of SSRI 	Under this option, cross-tapering cautiously may be suitable for SSRIs that do not interact with SNRIs. 
To another SNRI (duloxetine, venlafaxine)	**Option 1:** Direct switch if duloxetine dose <60 mg daily or venlafaxine dose <150 mg daily 	**Option 2:** Taper then start low dose of new SNRI 	Under this option, cross-tapering cautiously may be suitable. 

⚠ Paroxetine and fluoxetine (strong CYP2D6 inhibitors) may interact with duloxetine and venlafaxine.

⚠ Fluvoxamine (strong CYP1A2 inhibitor) may interact with duloxetine.

Additional notes:

- Option 1: While a similar mechanism of action may lessen discontinuation symptoms, patients who have taken an antidepressant for at least 6 weeks remain at risk of such effects. Alternative approaches that involve tapering can be considered.
- Option 2 is a more conservative strategy with the lowest risk of drug-drug interactions and additive adverse effects.
- Cross-tapering:
  - Entails gradually reducing the first medication while titrating up the new one from low dose, including a period in which both medications are taken.
  - Suitable patients are those able to manage complex medication regimen or have support from competent caregivers.

A note on switching from an SSRI or SNRI to other antidepressants (mirtazapine, agomelatine)[53,58,59,61]

- When switching to agomelatine or mirtazapine, the SSRI or SNRI should be tapered gradually (fluoxetine can be stopped, or tapered if dose ≥ 40mg daily). Some discontinuation symptoms may nonetheless be experienced as the mechanism of action is different.
- For SSRIs other than fluvoxamine: Taper then start agomelatine or mirtazapine at low dose; cross-tapering is possible.
- For fluvoxamine: Consider tapering fluvoxamine and stopping for 4–7 days (washout) before starting agomelatine, due to drug-drug interaction.

Supplement 3: GAD 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

- Assessment tools can inform the need for further evaluation, such as GAD-2 and GAD-7 scales, or the Edinburgh Postnatal Depression Scale (which contain questions on anxiety and thoughts of self-harm).[63]
- DSM or ICD criteria informs the diagnosis of GAD,[63] acknowledging that some symptoms can be challenging to distinguish from pregnancy-related features (e.g. fatigue, irritability, sleep disturbances). Worry can often include concerns for the baby/child, partner, and/or their own wellbeing.[64]
- In addition to typical mental state assessments for adults, additional factors for management planning include impact on mother-child bonding, obstetric health, breastfeeding status, risk of harm to self and others, experience of pregnancy/parenting (including specific stressors), social or partner support, and caregiving responsibilities.[63]

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

- For patients at mild severity, prioritise psychoeducation, addressing stressors and sleep disturbances, and psychological treatments.[65–67]
- For patients at higher severity, optimise decision-making by discussing treatment options, including medications (if used, note that international guidelines recommend SSRIs) and seeking specialist advice or referral.
- For patients already on existing medication for anxiety disorders, the risk of relapse or deterioration should be considered in deciding on the treatment strategy.

Considerations for use of antidepressants in perinatal GAD

	Benefits	Risks
Pregnancy	Relieve symptoms and improve functioning (limited direct evidence of efficacy,[68,69] extrapolated from the general adult population) Antenatal anxiety is associated with adverse outcomes such as postpartum depression,[70] and child behavioural and emotional symptoms.[71,72]	Individualised risk assessment is advised, given the uncertain and low-quality evidence.[68,73,74] Possible maternal and fetal adverse effects of SSRIs (e.g. postpartum haemorrhage, pre-term birth, poor neonatal adaptation syndrome) should be discussed with the patient, including the absolute risk (which can be low or rare).§
Postpartum	Relieve symptoms and improve functioning (limited direct evidence of efficacy,[68,69] extrapolated from the general adult population) Pospartum anxiety is associated with impaired maternal-infant bonding.[75]	In women who breastfeed, medication with minimal passage into breastmilk is preferred to reduce any adverse effects.** Sertraline is generally considered safe for breastfeeding.[76,77]

§ Whilst not developed specifically for the local population, references such as UK Teratology Information Service (UKTIS) and MotherToBaby may facilitate patient education and discussion.

** Overseas references such as MotherToBaby and LactMed may facilitate patient education and discussion on breastfeeding safety.

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

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)

Consider specialist involvement

Supplement 4: GAD 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 is important for case formulation and guides the need for referral.
  - This includes social, family, and educational context; developmental level, communication needs, and any learning disability; comorbidities; as well as any mental health problems faced by parents/caregivers/other family members.[78–80]
  - Psychosocial history-taking is often conducted in collaboration with schools and family members.
    - For adolescents, the HEEADSSS (Home, Education/Employment, Eating, Activities, Drugs, Sexuality, Suicidal ideation and Safety) framework can be considered.[81,82]
    - Sufficient time should be allocated for assessments.
- DSM or ICD criteria informs the diagnosis of GAD. Note that symptoms may present differently in children and adolescents, e.g. predominantly somatic symptoms, and the content of worries differ across developmental stages.

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

- Management of children and adolescents with anxiety symptoms will often involve coordinating with families, school personnel (e.g. counsellors, special education needs officers), specialised teams like REACH (Response, Early intervention and Assessment in Community mental Health), and/or social service agencies.
- Treatment is guided by issues identified during assessment and case formulation.
  - Psychoeducation and psychosocial support to address stressors are appropriate for all.
  - CBT adapted for the patient's age, developmental stage, and communication needs can be offered as first-line treatment.[83–85] Family therapy may be included to address parent and family-level factors that perpetuate anxiety.[86,87]
  - For children and adolescents at higher severity, specialist management or advice is needed to discuss the initiation of medication (e.g. an SSRI medication).[88,89] Note that this currently constitutes off-label use as local product inserts do not recommend use in patients under 18 years old.

Clinical and community resources

- School-based counselling services can provide access to multidisciplinary REACH teams. IMH, KKH, NUH REACH teams provide mental health assessment, holistic case management, and therapy services.
- Youth Integrated Teams (YIT) 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 (CREST-Youth) 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; IMH, Institute of Mental Health; ICD, International Classification of Diseases; KKH, KK Women's and Children's Hospital; NUH, National University Hospital

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Consider specialist involvement

References

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

Evidence-to-Recommendation Framework

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

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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 Guidances (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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