Evidence-to-Recommendation Framework

This document outlines the underpinning evidence and rationale for the recommendations in the ACE Clinical Guideline (ACG) ***Generalised anxiety disorder – easing burden and enabling remission***.

In ACGs, the strength of a recommendation reflects the confidence that the desirable effects of the recommended practice outweigh undesirable effects across the range of patients for whom the recommendation applies, based on the best available evidence:

- A strong recommendation is usually made when benefits clearly outweigh the risks, based on at least moderate-certainty evidence.
- A weak or conditional recommendation may be needed when there is a closer balance between benefits and harms, evidence is of low certainty, there is significant variability in patients' values and preferences, or important concerns with resourcing and feasibility of the recommended practice.[1]

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

Strength of recommendation: **Strong** Weak/conditional

Summary:
The Expert Group agreed to a strong recommendation for the approach to treatment planning. Initial stratification by severity allows healthcare providers to determine an appropriate treatment approach, in the context of tiered care. Patients' values and preferences for treatment are expected to vary significantly, and should therefore be taken into account during assessment. In terms of resource use and feasibility, incorporating patient preferences aligns with the principles and elements of patient-centred care, but may not be feasible in all situations.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
The treatment approach for GAD encompasses different treatment modalities (psychological treatment, medication), social care interventions, and measures for those at risk of harm to self (e.g. safety planning). When planning the treatment approach for GAD, initial stratification based on severity (of symptoms and functional impairment) is expected to improve access to appropriate treatment, by • helping identify patients in primary care who should be escalated to specialist care, and • enabling the assessment of benefit-risk ratio for prescribing medications such as selective serotonin reuptake inhibitors (SSRI) or serotonin	The recommendation incorporates the need to elicit and take into account the patient's values and preferences when selecting treatment approach, considering treatment modalities have different features, benefit-risk profiles, and suitability for the patient (further elaborated under Recommendations 2-4). Variability in patient preferences for assessment for treatment planning itself is not expected.

noradrenaline reuptake inhibitors (SNRI), or combination treatment, and • facilitating discussions with the patient to agree on a recommended treatment approach. The overlay of other factors acknowledges that the treatment plan should address the patient's overall condition, which will influence the site of care and treatment modality (including specific choice of medication).	
Certainty of evidence	**Resource use and feasibility**
Not applicable.[a]	Clinical assessment of severity is aligned with the National Mental Health and Wellbeing Strategy's tiered care model, around which the community-based ecosystem for management (spanning community services, social care, primary care, and specialist care) is being implemented nationally. The feasibility of eliciting patient preferences may vary depending on patient factors (e.g. health literacy, illness severity, age), clinician factors (e.g. communication skills, clinical experience), and the therapeutic relationship.[2]
Expert Group deliberation of above factors	
The Expert Group suggested that readiness to engage in treatment is distinct from patient needs and preferences, and should be incorporated into decision-making about treatment to increase the likelihood of adherence. In the context of psychotherapy, readiness has been conceptualised as "the willingness to engage, having coping skills, and safety and stability".[3]	

a. No effect estimate was generated for the clinical action of assessment of severity and other factors. However, indirectly, the certainty of evidence for possible interventions after assessment, under Recommendation 2, 3, and 4, was taken into account.

Recommendation 2	**For mild GAD:** **a) Consider CBT-based psychological treatments as first-line.** **b) Consider medication if psychological treatments are not feasible or acceptable.**

Strength of recommendation: Strong **Weak/ conditional**

Summary:

The Expert Group agreed to a weak recommendation for CBT-based psychological treatments as a first-line choice for mild GAD, based on likely significant variability in patient value and preference, and feasibility considerations that may arise (need for faster treatment, session attendance is inconvenient to the patient). Whilst both CBT-based psychological treatment and SSRI/SNRI medications are effective in GAD, the benefit/risk ratio is more favourable for CBT-based psychological treatments with at least moderate certainty of evidence. Medication (either a short course of hydroxyzine, if appropriate, or SSRI/SNRI medication) can be suggested if treatment is needed and psychological options are not feasible or acceptable.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
Benefits and harms were informed by two bodies of evidence: one on psychological treatments compared to either treatment-as-usual (TAU) or waitlist controls (WLC), and the other on SSRI or SNRI medication versus placebo pills. The same effect estimates were applied for both mild and moderate GAD. CBT reduced mean anxiety scores with a moderate effect size at endpoint (standardised mean difference [SMD] −0.68, 95% CI −1.05 to −0.32). The difference persisted three to twelve months after receiving the intervention (SMD −0.58, 95% CI −0.93 to −0.23).[4] The effectiveness of psychotherapy delivered in primary care settings is consistent across trials, with overlapping confidence intervals (SMD -0.49, 95% CI -0.88 to -0.1).[5] Adverse effects of psychotherapy are not systematically monitored in trials; these include unpleasant memories[6], unpleasant feelings[6], stress about homework, and not responding due to being unable/unwilling to engage with therapy (Expert Group input). Hydroxyzine reduced anxiety symptoms (SMD -0.42, 95% CI -0.62 to -0.21), and was not significantly different from benzodiazepines and buspirone.[7] No data on remission or comparison with SSRI/SNRI medication was available. The American Geriatrics Society Beers Criteria recommend	Psychological treatment: Significant variability between patient preference is expected, due to varying perceptions and expectations of psychological treatment[12], differences in treatment formats available depending on setting (group versus individual, blended versus face-to-face)[13], stigma, inconvenience, and scheduling issues.[14] Medication: Significant variability between patient preference is expected, as adverse effects may not be acceptable to all patients.[15] In one study, negative perceptions of medication for MDD and GAD were more commonly associated with some sociodemographic factors, e.g. older age, lower education level.[16]

hydroxyzine is avoided in older adults due to the risk of falls, delirium, and dementia.[8] SSRI and SNRI antidepressants reduced anxiety symptoms with similar efficacy between individual agents (mean difference [MD] on Hamilton Anxiety Rating Scale [HAM-A]: 2.29-3.13 points more than placebo).[9] Overall, antidepressants are more effective than placebo in increasing the rate of treatment response (reduction of HAM-A score by at least 50%).[10] However, an increased risk of adverse effects is also more likely. The number needed to harm (NNH) was 7 for ejaculation dysfunction, 12 for asthenia, 13 for somnolence, 14 for insomnia, and 16 for loss of libido. [11]	
Certainty of evidence	**Resource use and feasibility**
Within trials, to allow for subgroup analysis, studies did not differentiate outcomes by severity groups. Hence, evidence for mild GAD is derived from studies of participants with mild to severe symptoms (psychological treatments), and moderate to severe symptoms (SSRI or SNRI medication). • Moderate certainty of evidence for CBT's effectiveness on reduction in anxiety symptoms (downgraded due to risk of bias and heterogeneity). • Very low to moderate certainty of evidence for various SSRIs and SNRIs in reducing anxiety symptoms (due to risk of bias, heterogeneity, and/or incoherence). • Low certainty of evidence for hydroxyzine (due to risk of bias and imprecision).	Psychological treatments are subsidised, and efforts to scale up and upskill community mental health providers in CBT are ongoing under the National Mental Health and Wellbeing Strategy. In terms of feasibility to implement, barriers include scheduling issues and waiting time for psychological interventions if the healthcare professional assesses that faster treatment is required. For patients with mild severity, it is possible to offer interim measures such as general care and support (e.g. psychoeducation, self-help materials, and social care interventions). Hydroxyzine and most SSRI and SNRI medications are on the Subsidy Drug List. Fluoxetine, sertraline, and venlafaxine are on the Healthier SG medication list (as of Oct 2024).
Expert Group deliberation of above factors	
• The Expert Group noted ongoing capacity-building in the local context and varying patient preference with psychological treatment. The alternative of medication may be acceptable for some patients who find that psychological treatment does not align with their preference or needs. • The Expert Group also noted that in mild GAD, some patients may benefit from the help of social services to address life stressors, low socioeconomic status, and interpersonal conflicts. They agreed this can be included under 'General Care and Support'.	

Recommendation 3	For 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.

Strength of recommendation: a) **Strong** | Weak/conditional

b) Strong | **Weak/ conditional**

Summary:

The Expert Group agreed to a strong recommendation that either psychological treatment or an SSRI/SNRI medication are first-line choices for moderate GAD, based on the favourable balance of benefits and harms, and feasibility. Patient preference should be taken into account when discussing either treatment option. The Expert Group also agreed to a weak recommendation for a combination of both modalities as a first-line choice, based on very low certainty of evidence for incremental effectiveness compared to a single-treatment modality, insufficient data on harms, and higher treatment burden and cost.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
Benefits and harms were informed by two bodies of evidence: one on psychological treatments compared to either treatment-as-usual (TAU) or waitlist controls (WLC), and the other on SSRI or SNRI medication versus placebo pills. The same effect estimates were applied for both mild and moderate GAD. CBT reduced anxiety scores with a moderate effect size at endpoint (standardised mean difference [SMD] −0.68, 95% CI −1.05 to −0.32). The difference persisted 3 to 12 months after receiving the intervention (SMD −0.58, 95% CI −0.93 to −0.23).[4] Effectiveness of psychotherapy (predominantly CBT) delivered in primary care settings is similar across trials, with overlapping confidence intervals (SMD -0.49, 95% CI -0.88 to -0.1).[5] Adverse effects of psychotherapy are not routinely monitored in trials. SSRI and SNRI antidepressants reduced anxiety symptoms with similar efficacy between individual agents (mean difference [MD] on Hamilton Anxiety Rating Scale [HAM-A]: 2.29-3.13 points more than placebo).[9] Overall, antidepressants are more effective than placebo in increasing the rate of treatment response (reduction of HAM-A score by at least 50%).[10] However, an increased risk of adverse effects is also more likely. The number needed to harm (NNH) was	Psychological treatment: Significant variability between patient preference is expected[19], due to varying perceptions and expectations of psychological treatment[12], differences in treatment formats available depending on setting (group versus individual, blended versus face-to-face) [13], stigma, inconvenience, and scheduling issues.[14] SSRI or SNRI medication: Significant variability between patient preference is expected, as adverse effects may not be acceptable to all patients. In one study, negative perceptions of medication for MDD and GAD were more commonly associated with some demographic factors, e.g. older age, lower education level.[16] Combination treatment: Studies in depression and anxiety disorders suggest preference for combination treatment also varies between patients.[20, 21]

7 for ejaculation dysfunction, 12 for asthenia, 13 for somnolence, 14 for insomnia, and 16 for loss of libido. <u>Combination treatment</u> A small evidence base on combining psychological treatment and an SSRI or SNRI for GAD suggests comparative effectiveness range between no difference to better short-term response between 8 to 12 weeks. In patients with comorbid major depressive disorder (MDD), the favourable benefit-risk ratio (especially for moderately-severe and severe MDD[17]) can indirectly support consideration of potential benefit. No comparison of adverse effects was available. A trial involving children and adolescents (moderate severity of anxiety disorders and above) reported a higher number of adverse effects for treatment involving both modalities. However, the authors noted this arm also had a higher number of study visits for detection.[18] Most withdrawals from adverse effects were detected in the sertraline arm and placebo arm, rather than the combination arm.	
Certainty of evidence	**Resource use and feasibility**
Within trials, to allow for subgroup analysis, studies did not differentiate outcomes by severity groups. Hence, evidence for moderate GAD is derived from studies of participants with mild to severe symptoms (psychological treatments), and moderate to severe symptoms (SSRI or SNRI medication). • Moderate certainty of evidence for effectiveness of CBT (downgraded due to risk of bias and heterogeneity). • Very low to moderate certainty of evidence for different SSRIs and SNRIs (due to risk of bias, heterogeneity, and/or incoherence). • Very low certainty of evidence for combination treatment (due to risk of bias, imprecision, and indirectness).	Psychological treatments are subsidised, and efforts to scale up and upskill community mental health providers in CBT are ongoing under the National Mental Health and Wellbeing Strategy. In terms of feasibility to implement, barriers include scheduling issues and waiting time for psychological interventions if the healthcare professional determines that faster treatment is required. Depending on the care setting, resources such as Assessment & Shared Care Teams (ASCAT) are available to provide earlier access for moderate GAD. Most SSRI and SNRI medications are on the Subsidy Drug List. Fluoxetine, sertraline, and venlafaxine are on the Healthier SG medication list (as of Oct 2024). Combination treatment is feasible to implement in clinic settings with access to psychological services (either in-house or via referral) and where the patient is able and agreeable to also attend medical consultations for medication management.

Expert Group deliberation of above factors	
The Expert Group noted the limited evidence for combining psychological and medication treatment modalities to treat GAD, and provided examples of clinical need based on the group's collective experience.	

Recommendation 4	For severe GAD, offer a combination of CBT-based psychological treatment and SSRI/SNRI medication as first-line.

Strength of recommendation: **Strong** Weak/conditional

Summary:

The Expert Group agreed to a strong recommendation for a combination of psychological treatment and SSRI/SNRI medication over a single treatment modality, given the detrimental impact of severe GAD. Clinical experience informed the Expert Group's judgement, taking into account the very low certainty of evidence for incremental effectiveness compared to a single-treatment modality, insufficient data to compare harms, and likely higher treatment burden and cost. As such, the above considerations should be carefully discussed with the patient as an important part of shared decision-making.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
Evidence for combination treatment is limited. Compared to a single treatment modality alone, the effectiveness of a combination of psychological treatment and an SSRI or SNRI ranged between no difference to better short-term response between 8 to 12 weeks.[22, 23] In patients with comorbid major depressive disorder (MDD), the favourable benefit-risk ratio (especially moderately-severe and severe MDD[17]) can indirectly support consideration of potential benefit. No comparison of adverse effects was available. A trial involving children and adolescents (moderate severity of anxiety disorders and above) reported a higher number of adverse effects for combination treatment. However, the authors noted that this arm also had a higher number of study visits for detection.[18] Most withdrawals from adverse effects were detected in the sertraline arm and placebo arm, rather than the combination arm.	Due to the level of severity, there could be less variability in how patients value the benefits of combination treatment versus additive adverse effects. Though not specific to severe GAD, literature suggests dropout rates are not significantly higher with combination treatment.[24] However, individuals may vary in their preference due to the additional time, cost, and treatment burden.
Certainty of evidence	**Resource use and feasibility**
Very low certainty of evidence (due to risk of bias, imprecision, and indirectness).	Combination treatment is feasible to implement in clinic settings with access to psychological services (either in-house or via referral) and where the patient is able and agreeable to also attend medical consultations for medication management. Patients with severe GAD may also be referred to specialist care, or via resources such as Assessment & Shared Care Teams (ASCAT) to provide earlier access to

	treatment. Combination of CBT and antidepressants is not a novel approach and utilises subsidised treatment options.
Expert Group deliberation of above factors	
The Expert Group discussed potential risks if combination treatment is not offered as well as the current state of evidence versus common practice in this group of patients. In line with the clinical principle that intensity of treatment should be commensurate with severity, and based on clinical experience of using this treatment approach, the Expert Group agreed on a strong recommendation with additional remarks to clarify the underlying considerations for clinicians.	

Recommendation 5	**If treatment does not achieve adequate response in patients with GAD, assess possible reasons before considering modifying treatment or seeking specialist advice.**

Strength of recommendation: **Strong** Weak/conditional

Summary:

The Expert Group agreed to a strong recommendation to carefully assess the need to modify treatment or seek specialist advice. There was limited evidence to compare different second-line strategies. Options include switching to an alternative treatment modality, combining two modalities, and switching to another medication. From the perspective of primary care, the included options were deemed to have favourable benefit/risk ratio and are feasible to implement by the Expert Group for second-line treatment, with the possibility of seeking specialist advice for other strategies or a referral if required.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
In routine clinical practice, assessment of reasons for suboptimal response after an adequate trial is expected to identify patients for whom a change in treatment strategy and/or specialist advice may be beneficial. Poorly controlled symptoms and persistent functional impairment from staying on ineffective treatment is a significant undesirable consequence that can be averted by timely reviews of response. Reference guidelines highlighted various strategies for modifying treatment when initial choice is ineffective. Given limited trials for next-step strategies in non-responders, benefits and harms for modifying treatment were extrapolated from the general evidence base (not limited to non-responders).	Variability among patients in terms of values and preferences is not expected for assessment of non-response (as an aspect of routine care). Due to the differences between treatment modalities, patient values and preferences are likely to vary for deciding which treatment to switch to (as such, options are provided in supporting content).
Certainty of evidence	**Resource use and feasibility**
Not applicable[b]	Management of inadequate response is expected to utilise existing treatment options and referral pathways to specialists.
Expert Group deliberation of above factors	
The Expert Group discussed that response could be inadequate when the medication dose has not been optimised. They agreed that before modifying treatment is considered, possible reasons should be assessed. Furthermore, due to non-uniform definition of response in GAD, the Expert Group agreed to provide a practical guide to assessing response in the supporting content to operationalise the recommendation.	

b. No effect estimate was generated for the clinical action of assessment to consider a change in management strategy. However, indirectly, the certainty of evidence for possible treatment approaches, under Recommendation 2, 3, and 4, was taken into account.

Recommendation 6	**Continue treatment with an SSRI or SNRI for at least six months after remission is reached in patients with GAD.**

Strength of recommendation: **Strong** Weak/conditional

Summary:

The Expert Group agreed on a strong recommendation to continue SSRI/SNRI medication in remitted patients for at least another six months. The actual duration should be personalised, and a plan for discontinuation put into place.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
Participants who have achieved remission or responded to antidepressant treatment face a higher risk of relapse if treatment is discontinued, compared to those who continue treatment for an additional 6 to 12 months (odds ratio [OR] 4.2, 95% CI 2.42 to 7.28).[25] It is unclear if there are benefits from longer treatment duration >12 months. Paroxetine, duloxetine, venlafaxine, and sertraline are moderately to strongly associated with withdrawal syndrome. Reported cases with serious withdrawal reactions had longer treatment duration on average (25.5 months versus 17.9 months).[26] Insufficient data on relapse prevention outcomes precluded the development of a recommendation for psychological treatments. Nonetheless, psychological treatments can include relapse prevention and booster sessions.	Patient values and preferences for continuation of SSRI or SNRI treatment are likely to vary. The decision will require adequate support and information, as previous experiences with medication may lead to negative beliefs and expectations. Qualitative evidence indicates some patients expect to no longer experience adverse effects and regain independence with discontinuation.[27]
Certainty of evidence	**Resource use and feasibility**
Moderate certainty of evidence, due to the high risk of bias.	Most SSRI and SNRI medications are available on the Subsidy Drug List. Fluoxetine, sertraline, and venlafaxine are on the Healthier SG medication list (as of Oct 2024).
Expert Group deliberation of above factors	
The Expert Group discussed that remission is difficult to define in GAD and agreed that a working definition can be provided as a guide to implement this recommendation. Based on collective clinical experience, after completion of the additional 6-12 months, several factors to consider when deciding if treatment should be discontinued is suggested in supporting text.	

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

Strength of recommendation: **Strong** Weak/conditional

Summary:

The Expert Group agreed on a strong recommendation to not routinely prescribe benzodiazepines (BZDs) as initial treatment in GAD, taking into account the need for careful clinical assessment and patient education to minimise the risk of negative consequences. This recommendation does not apply to treatment-resistant GAD, which is outside of the ACG's scope.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
BZDs offer rapid anxiolytic effects that makes it useful for acute and severe symptoms.[9, 28] However, BZD carries risks of adverse effects (discontinuation rates are higher than placebo[9]) as well as potential overdose or fatality when co-administered with alcohol or opioids. A subset of patients may progress to long-term benzodiazepine (BZD) use, increasing their risk of dependence and potential for abuse, misuse, and addiction. In Singapore, an online panel survey found that 2.7% of participants reported lifetime misuse of diazepam, often obtained from medical prescriptions.[29] Dependence can result in serious withdrawal reactions if the drug is abruptly discontinued or tapered too quickly. A case series of post-marketing reports in the United States revealed that dependence could develop in as little as days to weeks.[30] BZD dependence severity correlated with antidepressant use, insomnia, and alcohol dependence in a Dutch cohort with depression and/or anxiety disorders.[31] <u>Bridging therapy for SSRI/SNRI treatment</u> There is insufficient evidence to comment on use of regular, daily dosing of benzodiazepine as bridging therapy during the initial weeks of antidepressant treatment for GAD. Studies in major depression[32] and panic disorder[33, 34] report mixed findings on limited samples.	Variability in patients' values and preferences is expected, as the rapid onset of action for some may outweigh the concerns of adverse effects for others.[35] If a BZD is prescribed, patient education on indication for use, limited duration, adverse effects, and tapering is essential.
Certainty of evidence	**Resource use and feasibility**
Low certainty of evidence for reduction in anxiety symptoms, due to high risk of bias, heterogeneity, and indirectness.	The current recommendation reinforces existing practice and is not expected to change resource use.

Very low certainty of evidence for harms, as these are derived from epidemiological and postmarketing studies.	
Expert Group deliberation of above factors	
The Expert Group noted the ACG's scope excluded treatment-resistant GAD and was limited to management of anxiety (excluding insomnia) in primary and generalist care. The Expert Group agreed on the phrasing "do not routinely prescribe" to capture that BZDs are not first-line for most patients in whom SSRI/SNRI medication and/or CBT-based psychological treatment are suitable. It also underscores the need for careful clinical assessment if a BZD is considered, such as for acute relief of severe symptoms. This position acknowledges that primary care typically manages mild to moderate cases, with specialist referral available when first-line treatments prove ineffective or poorly tolerated. The group noted that if prescribed, it is more common to provide a limited supply to relieve severe symptoms on as needed or PRN dosing, and rarely as a regular daily regimen that carries a higher risk of dependence.	

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