Evidence-to-Recommendation Framework

This document outlines the underpinning evidence and rationale for the recommendation statements in the ACE Clinical Guideline (ACG) "Major depressive disorder – achieving and sustaining remission".
In ACGs, the strength of 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	**Evaluate MDD severity based on** • **Symptom profile,** • **Functional impairment, and** • **Risk of harm (to self or others).**

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

Summary:
The Expert Group acknowledged the importance of first determining the severity of the current major depressive disorder (MDD) episode before deciding on the management approach. In addition to presenting symptoms, accounting for functional impairment and risk of harm was deemed essential to provide a comprehensive evaluation of severity.

Evidence-to-recommendation considerations

Balance of benefits and harms	**Values and preferences**
Determining the severity of the presenting MDD episode is a vital first step in clinical management and influences the intensity of treatment provided.[2-5] This approach is supported by current evidence, which indicates that initial depression severity is a predictor of treatment response and should be accounted for during initial assessment and treatment decision-making. The Clinical Outcomes in MEasurement-based Treatment (COMET) trial found that the odds of remission with pharmacotherapy for patients with MDD increased with lower baseline 9-item Patient Health Questionnaire (PHQ-9) scores. Compared to patients with a baseline PHQ-9 score of 20–27, patients with baseline PHQ-9 scores of 15–19, 10–14, and 5–9 were increasingly more likely to achieve remission (odds ratios (ORs) of 1.19, 1.99, and 3.55, respectively).[6] International manuals include both severity of symptoms and functional impairment as components of MDD severity.[7, 8] Accounting for risk of suicide is also important, as underscored by a local observational study that reported a significant association between MDD and suicidality. The study showed patients with MDD had almost 7-fold greater odds of history of attempting suicide compared to patients without MDD (OR: 6.96, 95% confidence interval (CI): 3.39 to 14.32).[9]	No significant concerns identified.
Certainty of evidence	**Resources and feasibility**
The underpinning evidence concerning MDD severity and suicide risk arises from observational data, which may potentially be affected by confounding bias. Nonetheless, recent high-quality international guidelines emphasise evaluating MDD severity to guide treatment approach[2-5] and highlight the importance of assessing risk of harm among patients with	No significant concerns identified. Presenting symptoms, functional impairment, and risk of harm are

depression.[3, 5]	already evaluated routinely as part of MDD clinical assessment.

Expert Group deliberation of above factors

The Expert Group agreed that MDD severity should be evaluated in terms of symptom severity, functional impairment and risk of suicide. In addition to depression symptoms' intensity, they noted that the duration of symptoms and features of other mental health comorbidities should also be accounted for. The umbrella term "symptom profile" in the recommendation statement was therefore used to reflect these considerations.

The Expert Group further raised that risk of harm to others should be assessed in addition to risk of self-harm. Accordingly, the third factor in the recommendation incorporates risk of harm to both self and others.

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

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

Summary:

The Expert Group assessed that in addition to MDD severity, other patient factors (for example, psychosocial stressors and treatment history) influence the overall treatment approach. Additional time would be required to review these factors with the patient. Nonetheless, such assessments are essential to providing personalised care — which is valued by MDD patients and will enhance their treatment journey. Therefore, a strong recommendation in favour of personalised treatment planning was made.

Evidence-to-recommendation considerations

Balance of benefits and harms	**Values and preferences**
Determination of MDD severity is an essential first step after diagnosis as it determines the treatment approach.[2-5] In addition, assessment of various other factors (such as psychosocial stressors and history of past episodes and treatment) is recommended.[3-5, 10] These assessments may also influence the treatment approach. For example, the presence of domestic instability as a psychosocial stressor could alert clinicians to additionally refer patients to social services (as a complement to clinical treatment).	A local qualitative study reported that patients with MDD value personalised care (for example, care that addresses psychosocial vulnerabilities).[11] Local patient values are therefore aligned with the recommended practice of tailoring the treatment approach.
Certainty of evidence	**Resources and feasibility**
While the above-mentioned local qualitative study had a small sample size (n=17), the principle of personalising care is in line with recent high-quality international MDD guidelines.[3-5, 10]	Additional consultation time may be required for assessment of patient factors (such as the presence of psychosocial stressors and treatment history).

Expert Group deliberation of above factors

The Expert Group agreed that treatment must be personalised to the individual patient. They emphasised that patient preference (between non-pharmacological and pharmacological treatment) should be accounted for as one of the patient factors assessed.

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

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

Summary:
The Expert Group assessed that for mild to moderate MDD, the benefit-harm balance was more favourable for psychological interventions (supportive counselling and psychotherapy) compared to antidepressants. This was driven by evidence of equal efficacy between these treatment options as well as consideration of potential adverse effects with antidepressants. Nonetheless, the group recognised that psychological interventions are not suitable for all patients and in such cases, antidepressants are an acceptable alternative. Overall, a strong recommendation in favour of psychological treatment over antidepressants was made for this patient population.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
Pooled randomised controlled trial (RCT) data indicates more favourable benefit-risk profile for psychotherapy compared to antidepressants. Psychotherapy and antidepressants are equally effective in remission rates,[12-14] though psychotherapy may be more effective in reducing depression symptoms long term.[13, 15] Further, there is greater risk of discontinuing treatment due to adverse effects from antidepressants (6%) compared to from psychotherapy (<1%).[12] Supportive counselling has proven to reduce depression symptoms, although it may be less efficacious than psychotherapy.[16]	Patient preferences between psychotherapy and antidepressants varied in international literature,[17-19] and no published local data was identified. The Expert Group shared that in their clinical experience, not all patients are willing to engage in therapy.
Certainty of evidence	**Resources and feasibility**
While most RCTs were at moderate to high risk of bias due to missing outcome data and selective reporting,[15] pooled estimates were precise and consistent (no marked heterogeneity).[13, 14] Although the proportion of RCTs from Asia was small (<10%),[15] systematic reviews of cognitive behavioural therapy (CBT) in Asian settings affirm that it improves depression symptoms in these populations as well.[20, 21] It is thus expected that psychotherapies are effective in the local context. ACE also considered the potential "therapist effect" of psychotherapy, where patient outcomes vary due to differences between therapists. Hence, it is possible that reported effect sizes of psychotherapy in RCTs (where there is often therapist training and monitoring)[22] may not translate in real-world settings.	No local cost-effectiveness study comparing psychotherapy and antidepressants was identified. Low certainty evidence from the United States indicates first-line CBT may be dominant compared to second-generation antidepressants at 5 years' time horizon (health care sector and societal perspective).[23] The Expert Group shared that currently, resource constraints (availability of services and waiting time) factor in the provision of psychotherapy at the primary care level.
Expert Group deliberation of above factors	
The Expert Group concurred with the evidence findings and agreed that psychological treatment should typically be offered instead of antidepressants for mild to moderate MDD. However, they noted that locally not all patients are receptive to therapy. They also considered that there are clinical scenarios where rapid management of symptoms is required and waiting for a therapy referral is not feasible, as well as cases where some symptomatic improvement with antidepressants is required before a patient can adequately engage in therapy. Therefore, the caveat "where feasible and acceptable" was added to the recommendation to acknowledge that antidepressants may at times be warranted for this population. Although supportive therapy may be less efficacious than psychotherapy, it was retained as an option in the recommendation given evidence of its overall efficacy, and limited availability of psychotherapy services locally.	

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.

Strength of recommendation (4a): **Strong** Weak/conditional

Strength of recommendation (4b): Strong **Weak/conditional**

Summary:
The Expert Group decided on a strong recommendation supporting a combination of an antidepressant with psychotherapy due to evidence of its superior efficacy over either modality alone. Psychotherapy alone was listed as an alternative treatment option, given its more favourable benefit-risk balance compared to treatment with an antidepressant alone. A weaker recommendation for treatment with an antidepressant alone was included, in recognition that not all patients may be willing or able to receive psychotherapy.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
A network meta-analysis of 101 RCTs found that a combination of psychotherapy and pharmacotherapy is superior to either modality alone for achieving remission – risk ratio (RR) compared to psychotherapy alone was 1.22 (95% CI: 1.08 to 1.39); RR compared to pharmacotherapy alone was 1.23 (95% CI: 1.09 to 1.39).[13] Psychotherapy and pharmacotherapy are equally efficacious, although the underpinning evidence base is more established for moderately severe depression (32 RCTs), compared to severe depression (4 RCTs).[13] Overall, the benefit-harm balance is more favourable for psychotherapy compared to antidepressants, given the greater risk of adverse effects with the latter.[12] Second-generation antidepressants are preferred over first-generation antidepressants[3-5] due to the latter's low therapeutic index, which results in a greater likelihood of toxicity,[4, 24, 25] as well as potentially serious adverse effects (for example, seizure and coma).[4]	Patient preferences between psychotherapy and antidepressants varied in international literature,[17-19] and no published local data was identified. The Expert Group shared that in their clinical experience, not all patients are willing to engage in therapy.
Certainty of evidence	**Resources and feasibility**
While most RCTs were at moderate to high risk of bias due to missing outcome data and selective reporting,[15] pooled estimates were precise and consistent (no marked heterogeneity).[13] Although the proportion of RCTs from Asia was small (<10%),[15] systematic reviews of CBT in Asian settings affirm that it improves depression symptoms in these populations as well.[20, 21] It is thus expected that psychotherapies are still effective in the local context. ACE also considered the potential "therapist effect" of psychotherapy, where patient outcomes vary due to differences between therapists. Hence, it is possible that reported effect sizes of psychotherapy in RCTs (where there is often therapist training and monitoring)[22] may not translate to real-world settings.	No local cost-effectiveness study comparing psychotherapy, antidepressants, and their combination was identified. The Expert Group shared that currently, resource constraints (availability of services and waiting time) factor in the provision of psychotherapy at the primary care level.
Expert Group deliberation of above factors	
The Expert Group considered the underpinning evidence and concluded that a combination of antidepressants with psychotherapy represented the most effective treatment option. Given the more favourable benefit-harm balance with psychotherapy compared to antidepressants, the former was preferred. Therefore a strong recommendation was made to offer either a combination of an antidepressant with psychotherapy, or psychotherapy alone, for patients with moderately severe and severe MDD. Nonetheless, recognising that not all patients will be receptive to psychotherapy and that there may be scenarios where psychotherapy is not feasible, a weaker recommendation for provision of an antidepressant alone was included.	

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

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

Summary:
The Expert Group considered that when initial treatment proves ineffective, a thorough evaluation of possible reasons contributing to the poor response is important before making treatment adjustments. This is because factors such as suboptimal adherence or psychosocial stressors may hinder treatment effectiveness, and addressing them may therefore improve patients' response.

Evidence-to-recommendation considerations

Balance of benefits and harms	**Values and preferences**
For cases where initial treatment is not effective, recent high-quality international MDD guidelines[3, 5] recommend to first assess and address underlying causes of treatment ineffectiveness such as the presence of psychosocial stressors, suboptimal treatment adherence, misdiagnosis (for example, missed diagnosis of bipolar disorder), and comorbid illnesses that may limit response to treatment (for example, anaemia, hypothyroidism, or psychosis). Notably, suboptimal adherence to antidepressant medication among patients with depression is common, with rates of 46% to 83% reported.[26] Thus, it is important to assess patients' adherence to antidepressant medication before deciding if a change in medication is required.	No significant concerns identified.
Certainty of evidence	**Resources and feasibility**
Not applicable.	No significant concerns identified.
Expert Group deliberation of above factors	
The Expert Group agreed with the principle that underlying reasons for treatment ineffectiveness should first be assessed, and where possible addressed, before adjusting the management strategy.	

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.**

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

Summary:
The Expert Group acknowledged that the treatment goal for MDD is not only to achieve remission, but also to sustain it by reducing the risk of relapse. As current evidence consistently reported reduced relapse risk when post-remission treatment is provided, a strong recommendation to continue treatment after remission was made. A duration of at least 6 months for post-remission antidepressant treatment was recommended because relapse occurs most frequently during this time.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
A systematic review found that compared to placebo, antidepressants reduce the risk of relapse by almost half (one-year relapse rate of 24% with antidepressants compared to 44% with placebo).[27] Similarly, a network meta-analysis (NMA) found that psychotherapy is more effective than control in preventing relapse and equally effective compared to antidepressants. This NMA also reported that a combination of psychotherapy and antidepressants was superior to psychotherapy alone (hazard ratio (HR): 0.59; 95% CI: 0.47 to 0.77) or antidepressants alone (HR: 0.58; 95% CI: 0.44 to 0.75). Psychotherapy with tapering of antidepressants was as effective as antidepressant treatment.[28] These results were congruent with other published systematic reviews.[29, 30] There was also no statistically significant difference in efficacy between structured psychotherapies and nonspecific, supportive psychotherapy.[28] If antidepressants were used during acute-phase treatment, continuing antidepressant treatment for at least 6 months post-remission is important because relapse occurs most frequently during this time.[27] Recent, high-quality international MDD guidelines advise maintaining the same dose that resulted in remission,[3, 4] unless adjustments are required (for example, due to adverse effects).[3]	The Expert Group raised that patients who achieve remission with one treatment modality (either psychological treatment or pharmacotherapy alone) may not be receptive to a combined treatment approach during the post-remission phase.
Certainty of evidence	**Resources and feasibility**
The protective effect of continuing antidepressants post-remission may be over-estimated in current evidence. Firstly, control groups (assigned to placebo) may experience antidepressant discontinuation symptoms, which may be misinterpreted for a depression relapse. Similarly, blinding of participants is more challenging in relapse prevention RCTs, as patients may infer their assignment to the placebo control group when they experience discontinuation symptoms.[27]	No significant concerns identified.
Expert Group deliberation of above factors	
The Expert Group agreed with the evidence findings and assessed that continuing treatment post-remission is important for reducing relapse risk. Although there was evidence to suggest that a combination of psychological treatment and antidepressants was superior to either modality alone in preventing relapse, the group assessed that patients may not be receptive to receiving a combined treatment approach after achieving remission via a single treatment modality. Therefore, the recommendation did not specifically promote a combination of psychological treatment and antidepressants for post-remission treatment.	

References

1. Schünemann H, Brożek J, Guyatt G, et al. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. 2013. Available from: https://gdt.gradepro.org/app/handbook/handbook.html#h.1yd7iwhn8pxp [Accessed 4 March 2025].
2. Qaseem A, Owens DK, Etxeandia-Ikobaltzeta I, et al. Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: a living clinical guideline from the American College of Physicians. Ann Intern Med. 2023;176(2):239-252.
3. National Institute for Health and Care Excellence (NICE). Depression in adults: treatment and management (NICE guideline NG222). 2022. Available from: https://www.nice.org.uk/guidance/ng222 [Accessed 3 March 2025].
4. Department of Veterans Affairs and Department of Defense (VA/DoD). VA/DoD clinical practice guideline for the management of major depressive disorder. Washington, DC: U.S. Government Printing Office. 2022.
5. Malaysian Health Technology Assessment Section (MaHTAS). Management of major depressive disorder (second edition). 2019. Available from: https://www.moh.gov.my/index.php/pages/view/3962 [Accessed 3 March 2025].
6. Yeung AS, Jing Y, Brenneman SK, et al. Clinical Outcomes in Measurement-based Treatment (Comet): a trial of depression monitoring and feedback to primary care physicians. Depress Anxiety. 2012;29(10):865-873.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition, text revision. Washington, DC, American Psychiatric Association. 2022.
8. World Health Organization. International Classification of Diseases, Eleventh Revision (ICD-11). 2024. Available from: https://icd.who.int/browse/2024-01/mms/en [Accessed 3 March 2025].
9. Ganesh KK, Abdin E, Vaingankar JA, et al. The relationship between suicidality and socio-demographic variables, physical disorders, and psychiatric disorders: results from the Singapore Mental Health Study 2016. Int J Environ Res Public Health. 2021;18(8):4365.
10. World Health Organization. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Geneva, World Health Organization. 2023.
11. Tan RXR, Goh YS. Perceptions of community mental health services among culturally diverse adult Singaporeans with major depressive disorder: a descriptive qualitative study. Int J Ment Health Nurs. 2024;33(1):143-158.
12. Gartlehner G, Dobrescu A, Chapman A, et al. Nonpharmacologic and pharmacologic treatments of adult patients with major depressive disorder: a systematic review and network meta-analysis for a clinical guideline by the American College of Physicians. Ann Intern Med. 2023;176(2):196-211.
13. Cuijpers P, Noma H, Karyotaki E, et al. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry. 2020;19(1):92-107.
14. Cuijpers P, Oud M, Karyotaki E, et al. Psychologic treatment of depression compared with pharmacotherapy and combined treatment in primary care: a network meta-analysis. Ann Fam Med. 2021;19(3):262-270.
15. Furukawa TA, Shinohara K, Sahker E, et al. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. World Psychiatry. 2021;20(3):387-396.
16. Cuijpers P, Miguel C, Ciharova M, et al. Non-directive supportive therapy for depression: a meta-analytic review. J Affect Disord. 2024;349:452-461.
17. Dorow M, Löbner M, Pabst A, et al. Preferences for depression treatment including internet-based interventions: results from a large sample of primary care patients. Front Psychiatry. 2018;9:181.
18. van Schaik DJ, Klijn AF, van Hout HP, et al. Patients' preferences in the treatment of depressive disorder in primary care. Gen Hosp Psychiatry. 2004;26(3):184-189.

19. Affengruber L, Wagner G, Dobrescu A, et al. Values and preferences of patients with depressive disorders regarding pharmacologic and nonpharmacologic treatments: a rapid review. Ann Intern Med. 2023;176(2):217-223.
20. Maddock A, Blair C, Ean N, et al. Psychological and social interventions for mental health issues and disorders in Southeast Asia: a systematic review. Int J Ment Health Syst. 2021;15(1):56.
21. Karat BG, Narikuzhy S, Bonato S, et al. The effectiveness of cognitive behavioral therapy interventions on depression and anxiety in the adult East Asian and related diaspora populations: a meta-analysis. Int J Cogn Ther. 2023;16(1):1-25.
22. Saxon D, Firth N, Barkham M. The relationship between therapist effects and therapy delivery factors: therapy modality, dosage, and non-completion. Adm Policy Ment Health. 2017;44(5):705-715.
23. Ross EL, Vijan S, Miller EM, et al. The cost-effectiveness of cognitive behavioral therapy versus second-generation antidepressants for initial treatment of major depressive disorder in the United States: a decision analytic model. Ann Intern Med. 2019;171(11):785-795.
24. McKenzie MS, McFarland BH. Trends in antidepressant overdoses. Pharmacoepidemiol Drug Saf. 2007;16(5):513-523.
25. Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. BMJ. 1995;310(6974):221-224.
26. Niarchou E, Roberts LH, Naughton BD. What is the impact of antidepressant side effects on medication adherence among adult patients diagnosed with depressive disorder: a systematic review. J Psychopharmacol. 2024;38(2):127-136.
27. Zhou D, Lv Z, Shi L, et al. Effects of antidepressant medicines on preventing relapse of unipolar depression: a pooled analysis of parametric survival curves. Psychol Med. 2022;52(1):48-56.
28. Zhou D, Zhou X, Lin Q, et al. Nonpharmacological interventions for relapse prevention in unipolar depression: A network meta-analysis. J Affect Disord. 2021;282:1255-1262.
29. Guidi J, Fava GA. Sequential combination of pharmacotherapy and psychotherapy in major depressive disorder: a systematic review and meta-analysis. JAMA Psychiatry. 2021;78(3):261-269.
30. Krijnen-de Bruin E, Scholten W, Muntingh A, et al. Psychological interventions to prevent relapse in anxiety and depression: A systematic review and meta-analysis. PLoS One. 2022;17(8):e0272200.