Evidence-to-Recommendation Framework for the 2026 ACE Clinical Guideline on management of mild and moderate dementia in older adults

This document outlines the underpinning evidence and rationale for the recommendation statements in the ACE Clinical Guideline (ACG) "Management of mild and moderate dementia in older adults".

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	**Assess cognition, function, and behaviour to prioritise treatment.**

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

Summary:
A strong recommendation was made for cognition, function, and behaviour to be assessed as core domains to guide dementia management. This was based on the domains' established impact on quality of life, extensively cited in clinical guidelines and studies, and practicality for assessment in primary care settings.

Balance of benefits and harms	
Cognition, function, and behaviour are three primary areas affected by dementia. Assessment of these domains inform staging which helps to identify and guide priorities for management. Improvements in one or more of these domains can significantly improve quality of life[2-5] and these domains have been extensively cited in published studies and international guidelines.	
Certainty of evidence	**Values and preferences**
Not applicable. This recommendation is a clinical practice principle, and the importance of assessing these domains is well-established in the literature and guidelines on dementia management.	No significant variability expected in patients' or carers' values regarding the importance of assessing these core domains. The specific assessment may need to be adapted based on patient and carer circumstances.
Resources and feasibility	**Acceptability and other considerations**
These domains are readily assessable in a primary care setting, often through patient and carer inputs (e.g. observations, verbal reports, self-assessment) or standardised scales and questionnaires, making them practical choices for routine evaluations. The recommendation intentionally avoids mandating the use of specific assessment scales to provide flexibility for healthcare professionals to tailor the assessment to suit different practice circumstances.	While assessment of these domains is generally acceptable to healthcare professionals and patients, language barriers may affect assessment accuracy, particularly if using standardised tools. Some patients or carers may be hesitant to report cognitive or behavioural changes due to stigma around dementia. Assessment quality may be affected by who attends the clinic visits, as different carers may have varying levels of familiarity with the patient's baseline function and daily patterns.
Expert Group deliberation of above factors	
The Expert Group agreed on the assessment of these three core domains while acknowledging practical implementation challenges in primary care settings. They emphasised that while formal assessment tools provided valuable objective measures, the approach should remain flexible and pragmatic to accommodate varying clinical settings and time constraints, hence the decision to provide examples of validated tools in the supporting text of the ACG without mandating specific ones. They highlighted that accurate assessment, particularly of behavioural symptoms, requires reliable carer input.	

Recommendation 2	a) Optimise control of vascular risk factors. b) Encourage participation in tailored non-pharmacological interventions to support cognition and function.

Strength of recommendation 2a): **Strong** Weak/conditional

Strength of recommendation 2b): **Strong** Weak/conditional

Summary:
A strong recommendation was made for a) vascular risk factor management and b) non-pharmacological interventions, as part of managing dementia. For a), a strong recommendation was made based on the benefits of optimising vascular health in alignment with existing clinical practice. For b), a strong recommendation was based on demonstrated benefits of various non-pharmacological interventions (including cognitive stimulation therapy, exercise, and music therapy), favourable safety profiles, and evidence showing greater effectiveness of multicomponent interventions.

Balance of benefits and harms

Recommendation 2a):

A comprehensive approach to vascular health is an essential component of dementia management.[6, 7] Active management of modifiable risk factors including hypertension, type 2 diabetes, dyslipidaemia, smoking cessation, and minimising alcohol intake can contribute to delayed disease progression in patients with dementia. While evidence on the direct impact of optimal vascular risk management on dementia progression remains limited, the established vascular benefits with minimal risk of harm support this approach. Additionally, the principles of dementia risk reduction through vascular health management may be reasonably extrapolated to support slowing disease progression in those already diagnosed with dementia.

Recommendation 2b):

High-quality, international guidelines (NICE 2018, and Malaysia 2021) have made overall positive recommendations on non-pharmacological interventions for function and cognition in patients with dementia.

- NICE 2018 recommends offering group cognitive stimulation therapy (CST); considering group reminiscence therapy (RT), and cognitive rehabilitation (CR) or occupational therapy to support functional ability (Rec 85).[8] No specific recommendation for physical exercise, music therapy, or art therapy was made, as these were instead grouped under "offer a range of activities tailored to individual preferences" (Rec 82; of note, the NICE guideline committee decided not to make a specific recommendation for/against physical exercise as the DAPA trial was still pending; for music therapy, they noted that the magnitudes of benefits were uncertain, and there was considerable variability in both the structure and intensity of the interventions tested). NICE recommends **against** cognitive training (Rec 88), acupuncture (Rec 86), ginseng or vitamin supplements (Rec 87), and non-invasive brain stimulation (Rec 90).
- Malaysia 2021 recommends that CST and physical activity should be offered for cognitive function in mild–moderate dementia;[9] while music-based therapy is not recommended (no statistically significant effect on cognition, low certainty of evidence). The Malaysian guideline defers to NICE 2018 for RT and CR.

In addition to high-quality guidelines, newer evidence has emerged to complement judgements on non-pharmacological interventions for dementia (e.g. the DAPA trial on physical exercise).

Based on international guidelines positions[8, 9] and overall availability/use in local context, ACE prioritised the following non-pharmacological interventions for detailed evidence review, with the intent of assessing their suitability as key examples in the ACG: cognitive rehabilitation (CR), cognitive stimulation therapy (CST), physical exercise, reminiscence therapy (RT), art therapy, and music therapy. Below is a summary of reported benefits, with full details of evidence and associated estimates in **Appendix 1**:

- CST: Compared to no cognitive stimulation, CST demonstrated statistically significant improvements in cognition (various scales/tools measurements, e.g. CST: compared to no cognitive stimulation or usual care, CST demonstrated statistically significant improvements in global cognition (MMSE, ADAS-Cog, CAM-COG; MD range 1.3–3.5 points across meta-analyses) and instrumental ADL (Lawton-Brody IADL and equivalents), with benefits maintained with continued delivery) including global cognition based on MMSE/MoCA; statistically significant improvements were also reported for language outcomes measured with narrative language test and working memory measured with Backward Digit Span. These cognitive benefits were maintained with continued delivery. For functional outcomes, CST demonstrated statistically significant

improvements in instrumental ADL, but not in basic ADL. Improvements at follow up varied (functional benefit beyond 10 months is less certain and may require maintenance sessions).[10]

- RT: Compared to control, RT demonstrated statistically significant improvements in global cognition (MMSE, MD 3.72) and memory (Memory Assessment Test, MD 2.14). Benefits were consistent across individual, group, and combined delivery formats. Executive function was not statistically significantly improved (Frontal Assessment Battery, MD 0.59, 95% CI: −0.17 to 1.35). No functional outcomes were assessed.[11]
- Physical exercise: Compared to control, physical exercise demonstrated statistically significant improvements in global cognition in Alzheimer's disease across aerobic exercise (MMSE, MD 2.95; Zhou 2022), resistance training (MMSE/MoCA/CAMCOG, SMD 0.60), and Tai Chi (MMSE, SMD 0.27). For functional outcomes, statistically significant improvements were observed in overall ADL (SMD 0.33) and instrumental ADL (SMD 0.36). Greater functional benefits were observed in multicomponent and aerobic exercise subgroups.[12-14]
- CR: Compared to inactive control, CR demonstrated statistically significant improvements in immediate memory (Rivermead Behavioural Memory Test – Second Edition [RBMT-II], MD 0.27). No statistically significant effects were found for delayed memory, global memory, verbal fluency, or working memory. For functional outcomes, CR demonstrated large, statistically significant improvements in personalised goal performance, both self-reported (SMD 1.46; 3 RCTs) and informant-rated (SMD 1.61; 3 RCTs), maintained at follow-up. No significant effect was found for general functional ability (SMD 0.05; not statistically significant). Gains were specific to practised goals and maintained at 3–12 months follow-up.[15]
- Art therapy: Compared to control (active or recreational activities), art therapy demonstrated no statistically significant effects on global cognition (MMSE).[16]
- Music therapy: Compared to control (usual care or other activities), music therapy demonstrated no statistically significant effect on global cognition (MMSE/SIB/ADAS-Cog, SMD 0.19, 95% CI: −0.01 to 0.40). Results were consistent across delivery subgroups.[17, 18]

Overall, evidence suggests that multicomponent approaches are more effective than single interventions,[19, 20] and that sustained duration (generally >6 months) produces greater benefit.[10]

All interventions reviewed above have favourable safety profiles. No serious adverse events were reported across studies of CST, RT, physical exercise, CR, art therapy, or music therapy. Minor harms associated with physical exercise (e.g. musculoskeletal discomfort, falls in frail participants) were infrequent and did not differ significantly from control conditions.

Certainty of evidence	Values and preferences
Recommendation 2a): Evidence on the direct impact of optimal vascular risk management on dementia progression remains limited. However, published best practices globally recommend optimising vascular conditions based on the established benefits for vascular health which may slow disease progression. **Recommendation 2b):** The certainty of evidence for the non-pharmacological interventions reviewed ranged from very low to high, varying depending on intervention type and outcomes assessed. The certainty of evidence of outcomes is listed below, by intervention type: • CST: moderate certainty for global cognition; high certainty for instrumental ADL; moderate certainty for basic ADL (CI crosses zero, not statistically significant); very low certainty for language and working memory. • RT: high certainty for memory; moderate certainty for global cognition and executive function (executive function CI crosses zero, not statistically significant)	**Recommendation 2a):** No significant concerns identified, widely accepted as part of the overall management to optimise vascular risk in patients with dementia. **Recommendation 2b):** Cognition and function are outcomes of high importance to patients with dementia and their caregivers. Maintaining cognitive ability and independence in daily activities aligns with patient priorities for quality of life and continued meaningful participation.[21] Where evidence is available only for cognitive outcomes (e.g. RT) or only for functional outcomes (e.g. CR), the benefit remains relevant and meaningful to patients provided the specific goal of the intervention is understood and communicated at the point of referral.

- Physical exercise: moderate certainty for global cognition* (aerobic exercise, resistance training, Tai Chi); low certainty for overall ADL and instrumental ADL; very low certainty for basic ADL.
- CR: high certainty for personalised goal performance (self-reported and informant-rated); high certainty for immediate memory; low to very low certainty for other cognition outcomes (delayed memory, verbal fluency, working memory; not statistically significant); low certainty for general functional ability (not statistically significant)
- Art therapy: very low certainty for global cognition
- Music therapy: low certainty for global cognition (not statistically significant)

Further details are available in **Appendix 1** (evidence tables). None of the outcomes studied for music and art therapy reached moderate certainty of evidence.

Common study limitations included heterogeneity due to inconsistency of effects and imprecision of findings, small sample sizes, wide confidence intervals with variation in participant characteristics and intervention parameters, and risk of bias (including inadequate reporting of random sequence generation).

Resources and feasibility	Acceptability and other considerations
Recommendation 2a): Optimising multiple vascular risk factors may require additional clinic visits and coordination between healthcare providers, potentially straining limited primary care resources. Time constraints during consultations can make comprehensive management of multiple conditions challenging. While most interventions can be implemented within existing primary care settings, there may be limited access to some lifestyle interventions such as structured exercise programs or intensive smoking cessation support. **Recommendation 2b):** Locally, there may be challenges for patients to access non-pharmacological interventions. These interventions are currently offered in tertiary settings or through various community support services and programmes, such as Community Outreach Team (CREST), Community Intervention Team (COMIT), Dementia Day Care Centres, Active Ageing Centres, and Community Centres.[22] Transport accessibility and cost considerations may also affect participation in community-based services and programmes.	**Recommendation 2a):** Several factors may affect patient acceptance of and adherence to vascular risk management. Cognitive impairment can impact patients' ability to follow complex medication schedules or lifestyle changes, while increased medication burden from managing multiple conditions may reduce adherence.[23] Patients or carers may prioritise dementia-specific treatments over other health conditions, particularly when the connection between vascular risk and cognitive decline is not clear.[24] Lifestyle and dietary modifications can be challenging as long-standing habits are difficult to change, and exercise initiatives may be limited by mobility concerns or motivation issues. Family dynamics often play a crucial role, as modifications to shared behaviours (e.g. dietary habits) often require support from the household. **Recommendation 2b):** Language barriers need to be considered, and some interventions may need to be modified to suit individual patient's preferences. The success of interventions may depend on carer availability and engagement.

Expert Group deliberation of above factors

The Expert Group strongly supported both components of this recommendation based on the favourable benefits-harms ratio and the certainty of the evidence. They noted the role of vascular risk management in delaying disease progression and its alignment with existing clinical practice. They recommended maintaining a flexible approach to implementation, acknowledging key challenges including cost, accessibility, language barriers, and carer availability. The Expert Group agreed that interventions should be tailored to individual preferences and circumstances to optimise engagement and outcomes, particularly given the varying levels of evidence for different intervention types.

For examples to be cited in **Table 2**, the Expert Group noted the principles for selection and agreed on listing cognitive stimulation therapy (CST), reminiscence therapy (RT), physical exercise, and cognitive rehabilitation (CR) given the moderate certainty of evidence for cognition or function outcomes in patients with Alzheimer's disease, vascular dementia, or mixed dementia. Art therapy and music therapy were reviewed but did not meet the moderate-certainty threshold for cognition or function in the target population and are therefore not included in Table 2.

* Conflicting GRADE assessments between sources for aerobic exercise in AD; see **Appendix 1** for full details; note on study selection for physical exercise CoE: Where two sources cover the same intervention-outcome pair, ACE selects the source whose inclusion criteria most closely match the target population (patients with Alzheimer's disease, vascular dementia, or mixed dementia), irrespective of which source yields higher CoE. Yang 2025 was reviewed but has broader inclusion criteria encompassing MCI and healthy older adults with cognitive decline alongside dementia, introducing indirectness as a GRADE downgrade domain for our target population. The primary source selected covers patients with dementia specifically, avoiding this indirectness penalty, hence providing a higher CoE. This principle is applied consistently across all interventions — see the corresponding note for art therapy (Deshmukh 2018 preferred over Masika 2020), where the same selection principle resulted in a *lower* CoE being reported: Deshmukh 2018 (Cochrane SR, 2 RCTs, n=60) was selected as the primary source as it applied GRADE formally, focused exclusively on dementia populations, and is a Cochrane-quality review. Masika 2020 (SR+MA, 4 RCTs, n=198) was identified but has broader inclusion criteria encompassing populations beyond dementia (including MCI and healthy older adults), reducing applicability to the target population. Where a more focused, higher-quality source is available, it is preferred even if it yields a lower CoE estimate. The lower CoE from Deshmukh 2018 is therefore the more accurate and applicable rating for this target population.

Recommendation 3	a) For patients with mild or moderate Alzheimer's disease, consider an AChE inhibitor. b) For patients with moderate Alzheimer's disease, consider memantine as monotherapy if an AChE inhibitor is not tolerated, or in combination with an AChE inhibitor.

Strength of recommendation 3a): Strong **Weak/conditional**

Strength of recommendation 3b): Strong **Weak/conditional**

Summary:
Conditional recommendations were made. For acetylcholinesterase (AChE) inhibitors, this was based on modest but consistent benefits in cognitive outcomes, balanced against potential adverse effects in mild or moderate Alzheimer's disease. For memantine, the evidence supports its use in moderate Alzheimer's disease, either as monotherapy when an AChE inhibitor is not tolerated, or combined with an AChE inhibitor. Memantine has a more favourable safety profile than AChE inhibitors in moderate Alzheimer's disease, though it can still cause adverse effects including dizziness, headache, and somnolence. The conditional nature of the recommendations acknowledges the balance between the moderate- to high-certainty of evidence versus the adverse effects profile of the medications, and hence the need to consider individual patient factors, comorbidities, and existing medications when making treatment decisions.

Balance of benefits and harms

Recommendation 3a):
AChE inhibitors demonstrated modest benefits in cognitive outcomes, with significantly lower rates of cognitive decline (Mini-Mental State Examination [MMSE] loss of 0.2 to 1.37 points/year) compared to untreated patients with Alzheimer's disease (MMSE loss of 1.07 to 3.4 points/year).[25] Overall, the three AChE inhibitors (donepezil, rivastigmine, and galantamine) had similar efficacy in supporting cognition in patients with Alzheimer's disease.[26] In real-world settings, treatment with AChE inhibitors was associated with a slower cognitive decline, measured by stabilised MMSE scores, and reduced mortality over ~8 years.[25, 27] Studies have reported higher withdrawal rates (all-cause or adverse events-related discontinuations) with increased doses of AChE inhibitors, across all three medications. The most commonly reported adverse events across all three medications are gastrointestinal symptoms including nausea, vomiting, and diarrhoea.

Recommendation 3b):
Memantine monotherapy: Memantine showed efficacy in moderate (and severe) stages of Alzheimer's disease, with a favourable safety profile compared to placebo. Two network meta-analyses[28, 29] and a Cochrane review[30] reported that compared to placebo, memantine monotherapy provided improved cognition, function and behaviour in moderate (and severe) dementia. Other benefits included reduced risk of death, based on evidence from two retrospective studies, including data from electronic health records.[31, 32] There is currently very limited evidence of efficacy for memantine in mild Alzheimer's disease.[30] Memantine is generally well-tolerated, with a Cochrane review reporting that memantine did not significantly differ from placebo in overall adverse event rates (risk ratio [RR] 1.03, 95% confidence interval [CI] 1.00 to 1.06), regardless of dementia type or severity.[30] Memantine is 1.6 times more likely than placebo to result in dizziness (6.1% versus 3.9%), with 1.3-fold increased risk of headache (5.5% versus 4.3%), but no difference in falls.[30] A 2020 network meta-analysis concluded that while all treatment regimens were generally well tolerated, memantine emerged as the best-tolerated medicine, followed by placebo and the combination of memantine with donepezil.[29]

Memantine in combination with AChE inhibitors: When added to AChE inhibitors, memantine demonstrates modest improvements in cognition, function, and behaviour for moderate (and severe) dementia, without significantly increasing adverse events. The evidence for the added benefits of memantine is generally consistent across multiple studies, although some variability exists in the magnitude of effect and specific outcomes reported.[8, 28-30] Other benefits included reduced risk of death.[31, 32] There are no reported increase in adverse events from adding memantine to an AChE inhibitor. Long-term safety data supports the tolerability of both monotherapy and combination approaches, though individual patient responses may vary. Real-world data over 20 years on long-term safety of donepezil combined with memantine in patients aged more than 65 years revealed dizziness, somnolence, and

tremor as the most common adverse effects.[33]

Certainty of evidence	Values and preferences
Recommendation 3a): The certainty of evidence is moderate to high for cognitive benefits, with lower certainty for functional outcomes for all AChE inhibitors.[26] Studies generally showed low risk of bias, though there were some concerns on allocation concealment and differences in randomisation methods.[25-27] Key trials provided limited evidence beyond six months. Heterogeneous study designs (including variations in participant characteristics, severity of dementia, and dosages of AChE inhibitors) may affect generalisability of findings. **Recommendation 3b):** There is moderate-certainty evidence for efficacy of memantine and high-certainty evidence for safety outcomes.[8, 28-30, 33] Most studies showed a low risk of bias, though some had high risk of selection bias due to large differences in baseline outcomes that were as large or larger than the effect size for most outcomes. A few studies showed high risk of detection bias.	Patients' (and carers') preferences are likely to vary based on the experienced benefits versus adverse effects, administration route preferences, and availability or access considerations. Transdermal options may improve adherence where available.
Resources and feasibility	**Acceptability and other considerations**
Recommendation 3a): All AChE inhibitors (i.e. donepezil, rivastigmine, and galantamine) are approved for use in mild and moderate Alzheimer's disease. Donepezil is listed on the government subsidy list and Healthier SG Medication List. **Recommendation 3b):** Memantine is approved for use in moderate and severe Alzheimer's disease. Memantine is listed on the government subsidy list and Healthier SG Medication List.	Clear communication about realistic treatment expectations is essential, as some patients or carers may have overly optimistic expectations about medication benefits – AChE inhibitors and memantine are symptomatic treatment and are not a cure. The need for long-term treatment and associated costs may affect adherence.
Expert Group deliberation of above factors	
The Expert Group acknowledged the modest effect sizes but consistent benefits of AChE inhibitors and memantine. They highlighted the importance of shared decision-making, considering individual patient factors such as comorbidities, existing medications, and carer support; they also emphasised the need for clear guidance on dosing, titration, monitoring, and adverse effects. They noted that memantine's favourable safety profile supports prescribing based on the experience and comfort level of healthcare professionals in primary care, though specialists may be consulted as required.	

Recommendation 4	**Consider deprescribing AChE inhibitors or memantine when the overall benefits are no longer apparent to justify continued use.**

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

Summary:
A conditional recommendation was made for deprescribing AChE inhibitors or memantine, reflecting the complexity of discontinuation decisions. While evidence suggests that discontinuation may lead to more rapid cognitive and functional decline, particularly in the long term, the certainty of this evidence is generally low to moderate, and it can be challenging to distinguish between the effects of medication withdrawal and natural disease progression. The conditional recommendation reflects the need to balance potential benefits of reduced medication burden and adverse effects against the risk of accelerated symptoms of decline, whilst recognising significant variability in patients' and carers' values regarding treatment continuation versus discontinuation. This approach also acknowledges the absence of an optimal treatment duration, hence the decision to continue or discontinue must be tailored to suit the patient and their circumstances.

Balance of benefits and harms

Two systematic reviews have highlighted the need for individualised decisions about stopping AChE inhibitors based on patients' and families' preferences and values, and a balanced discussion of potential risks and benefits to discontinuation.[34, 35] In line with this individualised approach, the reasons to consider deprescribing may vary depending on the existing duration of treatment based on the Sydney 2018 guidelines.[36]

Considerations to deprescribe include when patients or carers decide to discontinue, adverse effects are intolerable, adherence cannot be achieved, drug interactions pose risks, or when non-dementia terminal illness is present. Additional considerations for patients treated for 12 months or more include clinically meaningful worsening over six months (excluding other medical causes), sustained decline, no observed benefit during treatment, or progression to severe dementia with dependence in most activities of daily living and limited environmental responsiveness.

Potential benefits of discontinuation include reduced adverse effects, decreased medication burden, and lower treatment costs, which may contribute to improved quality of life.

The risk of adverse drug withdrawal events can be reduced if treatment is discontinued gradually. Evidence from discontinuation studies suggest that stopping AChE inhibitors does not significantly increase adverse events or mortality compared to continuing AChE inhibitors (low certainty evidence).[34] However, discontinuation of an AChE inhibitor or memantine may lead to worsening symptoms of cognition, function, or behaviour (with very low- to moderate-certainty) compared to those who continue treatment. It may be challenging to distinguish between effects of medicine withdrawal and natural disease progression.[34, 36]

Certainty of evidence	**Values and preferences**
The seven randomised controlled trials (RCTs) included in a Cochrane review varied in rate of withdrawal (abrupt versus stepwise), severity of Alzheimer's disease, and study duration (6 weeks to 12 months).[34] Some studies were assessed to have high risk of selection, performance, detection, attrition, or reporting bias. Certainty of evidence varied by outcome type and time point, ranging from very low to moderate.[abc] For the other systematic review which evaluated practice guidelines recommendations, null findings and lack of	Patients' and carers' preferences regarding deprescribing are likely to vary. Some patients and carers may view medication discontinuation as abandoning treatment or "giving up" on the condition, while others may welcome reduced medication burden and potential adverse effects. Preferences may also be affected by previous experiences with medication benefits or adverse effects, and the perceived symbolic importance of continuing dementia-specific medication.

[a] Cognition: short term, worse with discontinuation (low certainty); medium term, uncertain effect (very low certainty); long term, worse with discontinuation by 2.09 standardised MMSE points (moderate certainty).
[b] Function: short term, little to no difference (low certainty); medium term, uncertain effect (very low certainty); long term, greater impairment with discontinuation by 3.38 Bristol Activities of Daily Living Scale points (moderate certainty).
[c] Behaviour: short and medium term, worsening of symptoms (low certainty); long term, little to no change (moderate certainty).

standardisation across endpoints made it difficult to draw robust conclusions about benefits of AChE inhibitor treatment on function and behaviour.[35] Heterogenous study designs such as duration of treatment and studied outcomes before deprescribing contributed to inconsistent findings.	
Resources and feasibility	**Acceptability and other considerations**
No significant concerns identified. Healthcare professionals who did not initiate the treatment may not be comfortable to raise the possibility of deprescribing. Gradual withdrawal protocols and close monitoring during the deprescribing process require additional clinical resources and follow-up arrangements.	Individual beliefs regarding the perceived value of persevering with treatment despite any observable benefits will influence acceptance of deprescribing and related discussions. The timing and approach to deprescribing discussions may need to be tailored based on family readiness and coping mechanisms.
Expert Group deliberation of above factors	
The Expert Group acknowledged that deprescribing decisions may be complex and require careful consideration of multiple factors. While potential benefits including reduced adverse effects and medication burden were noted, they noted the need for an individualised approach based on patients' and families' preferences, with clear guidance on when and how to approach deprescribing discussions.	

Recommendation 5	a) Identify and address underlying modifiable causes of BPSD. b) Prioritise tailored strategies as initial treatment for BPSD.

Strength of recommendation 5a): **Strong** Weak/conditional

Strength of recommendation 5b): **Strong** Weak/conditional

Summary:
Strong recommendations were made for a) identifying modifiable causes of behavioural and psychological symptoms of dementia (BPSD) and b) prioritising strategies as first-line treatment. For a), the strong recommendation reflects its essential role in improving outcomes by addressing unmet needs and potentially avoiding unnecessary medication use. For b), the strong recommendation was based on the more favourable safety profile of strategies compared to pharmacotherapy.

Balance of benefits and harms

Recommendation 5a):
It is widely accepted that BPSD may be a patient's expression of unmet needs, often communicated non-verbally.[37] The benefits of identifying and addressing the main source of distress include reduced BPSD, improved quality of life, and potentially decreased need for pharmacological interventions.[38, 39] Investigating these causes require time (to observe and document behaviour patterns), and may cause initial embarrassment or reluctance to discuss during assessment. However, failure to identify and resolve underlying causes may lead to inappropriate medication use, prolonged distress, and worsening symptoms.

Recommendation 5b):
Prioritising tailored strategies (e.g. physical exercise, craft activities) as first-line treatment for BPSD can effectively reduce challenging behaviours while avoiding medication-related adverse effects. Also, successful implementation can improve quality of life and enhance engagement in meaningful activities.[40, 41]

Compared to pharmacological approaches, behavioural strategies carry minimal risk and can lead to sustained improvements in behaviour. These approaches can reduce the need for medication, avoiding potential adverse effects associated with pharmacotherapy.

Certainty of evidence

Recommendation 5a):
Not applicable. This recommendation relates to a clinical practice principle.

Recommendation 5b):
The certainty of evidence overall for various behavioural strategies range from low- to high-certainty.[18, 42-63] Limitations stem primarily from varied study designs, small sample sizes, and high attrition rates among the older adults. These factors complicated the interpretation of treatment effects and meta-analyses, making consistent comparison challenging.

Values and preferences

Recommendation 5a):
No significant variability expected in patients' or carers' values regarding the importance of identifying underlying causes of BPSD. The specific assessment approach may need to be adapted based on individual patient circumstances and availability of inputs from the main carer.

Recommendation 5b):
Significant variability in preferences for these strategies is likely, influenced by the nature and severity of BPSD. Previous experiences with strategies and carer capacity to implement may impact acceptability.

Resources and feasibility

Recommendation 5a):
Identifying modifiable factors may be achieved through practical, low-cost methods such as sharing photos or videos of the patient's environment and routines with healthcare professionals and using simple behaviour tracking tools. The main resource implications are staffs' and carers' effort and time to trial the impact and

Acceptability and other considerations

Recommendation 5a):
The success of identifying modifiable causes depends on the main carer's observational skills and willingness to implement modifications. When multiple carers are involved, ensuring consistent observation and reporting can be challenging, as different family members may have varying perspectives on what constitutes

effectiveness of various modifications, and basic documentation tools to record details on what has been tried. **Recommendation 5b):** Main challenges include the time and resources required to develop and implement personalised strategies, the need for consistent implementation and therefore staff training and family education, and initial trial-and-error periods to find effective approaches. While strategies may not always be successful in addressing certain BPSD (e.g. constant vocalisations where the patient keeps shouting and the underlying cause is not identifiable), these strategies should nonetheless be attempted before pharmacotherapy where possible. Family dynamics and living arrangements may affect the feasibility of certain behavioural strategies. Costs of enrolling patients into structured programmes are also a consideration for long-term adherence. The revised **Annex E Table S5** provides a structured carer-facing reference for implementing strategies at home with basic instruction from a healthcare professional. The table is organised by BPSD type, with a column identifying commonly reported underlying triggers to assist carers in recognising and addressing modifiable causes before selecting a strategy. It is designed to complement **Figure 3** (BPSD assessment and management pathway) and the Sunflower Tool (**Annex D**) as part of a carer-led first-line approach consistent with Recommendation 5b.	concerning behaviour. Some carers may be reluctant to document or discuss certain behaviours due to embarrassment, particularly regarding personal care issues or aggressive behaviours. Clear communication about the iterative nature of this process is essential, as some families may have unrealistic expectations about immediate resolution of behaviours once causes are identified. **Recommendation 5b):** The success of strategies depends on consistent implementation across all carers and may require trial and error before effectiveness is established. Some families may struggle with the time investment required, particularly during initial implementation. Patient response to strategies vary based on personality, interests, and dementia stage, requiring ongoing adaptation of strategies as the condition progresses. Some patients may initially resist new approaches, necessitating patience and persistence from carers before benefits become apparent.

Expert Group deliberation of above factors

The Expert Group agreed on prioritising non-pharmacological approaches to managing BPSD due to their favourable benefit-harms ratio. This initially involves identifying and addressing modifiable causes of BPSD, as doing so may remove the need for further intervention. While behavioural strategies should follow, their implementation needs to be flexible based on individual circumstances and available resources. This stepped approach ensures that underlying causes are addressed before moving to more complex behavioural strategies.

The Expert Group endorsed an approach to **Annex E Table S5** which focuses on strategies implementable by carers in the home setting, thereby excluding interventions that require clinical training, prescribing authority, specialist equipment, or clinical assessment processes. Under this approach, **Table S5** is organised by frequently encountered BPSD with examples of commonly reported underlying triggers to help carers link observed behaviours to modifiable causes before selecting a strategy. Strategies were selected based on at least one published study demonstrating benefit, or sound practical rationale with a favourable safety profile.

Recommendation 6	**If BPSD persist and are significantly affecting the patient or others, consider prescribing tailored pharmacotherapy to address specific symptoms.**

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

Summary:
A conditional recommendation was made for tailored prescribing for persistent BPSD after addressing modifiable causes and attempting behavioural strategies. The strength of this recommendation reflects a need to prompt careful assessment of patient circumstances and needs, choosing symptom-targeted pharmacological approaches that balance potential benefits against medication-related risks whilst allowing clinical flexibility. Furthermore, outcomes, values and preferences, and acceptability of treatments are expected to vary significantly.

Balance of benefits and harms

The benefits of tailored pharmacotherapy for persistent BPSD include targeting specific symptoms that significantly impact the patient's quality of life and carer burden, potentially reducing overall medication burden through focused treatment, and allowing clinical flexibility to choose from available pharmacological options based on patient-specific factors. Not all BPSD will respond to medications (e.g. wandering, hoarding, repetitive behaviours may be better managed through non-pharmacological approaches), hence the need to avoid unnecessary medication exposure. The approach also recognises the complexity of off-label use. Overall, there are no medications with clear, favourable balance of benefits or harms in addressing any of the BPSD. Off-label options report inconsistent efficacy for BPSD and their benefits are often not clinically significant. Further details on the medication classes included are as follows:

Cognitive enhancers

Agitation

AChE inhibitors (donepezil, galantamine, rivastigmine): mixed efficacy for overall BPSD in moderate Alzheimer's disease, not clinically meaningful.

- No clinically meaningful benefits for agitation for 10 mg/day donepezil compared to placebo in Alzheimer's disease after 24 to 26 weeks of treatment.[64]
- Common adverse effects include gastrointestinal symptoms (nausea, vomiting, diarrhoea); in some patients, AChE inhibitors may paradoxically worsen neuropsychiatric symptoms (anorexia, agitation, anxiety, confusion and disorientation, depression, psychosis, and sleep disturbances).[65, 66]

Memantine: mixed efficacy depending on patient population, results are inconsistent.

- Pooled analyses (3 RCTs, 6 months, placebo-controlled, n = 1826 patients with moderate to severe Alzheimer's Disease, MMSE score <20) reported modest benefits for agitation or aggression and psychosis with 20 mg/day memantine compared to placebo.[67, 68] Memantine may provide better efficacy in patients with high baseline agitation compared to lower baseline agitation.
- Cochrane review reported small clinical benefit of memantine compared to placebo for BPSD.[30]
- Memantine is well-tolerated (memantine > placebo > combination of memantine and donepezil), with no significant difference from placebo in overall adverse event rates (RR 1.03, 95% CI 1.00 to 1.06), regardless of dementia type or severity.[29, 30] Main adverse effects are dizziness and headaches.

Second-generation antidepressants

Agitation

- Mixed efficacy between individual selective serotonin reuptake inhibitors (SSRIs): when compared to placebo, citalopram demonstrated significantly higher efficacy for reducing agitation in dementia (standardised mean difference [SMD] -0.44, 95% CI -0.72 to -0.16), while sertraline (SMD -0.08, 95% CI -0.43 to 0.27) and fluoxetine (SMD 0.31, 95% CI -0.87 to 1.49) showed no significant difference in efficacy.[69] However, a 2011 Cochrane review reported that sertraline was associated with a reduction in agitation compared to placebo.[70]
- Mirtazapine showed no significant difference in reducing agitation compared to placebo, as reflected in the HTA-SYMBAD[d] trial.[69, 71]

[d] HTA-SYMBAD trial: 2023 National Institute for Health and Care Research (NIHR) Health Technology Assessment – Study of Mirtazapine for Agitated Behaviours in Dementia trial

Depression and anxiety (in patients with dementia)

- The precise aetiology of depression in dementia remains uncertain, though various mechanisms have been proposed.[72]
- Evidence suggests little possible benefit from SSRIs in reducing depression or anxiety for patients with dementia. Systematic reviews and meta-analyses reported mixed efficacy in treating depression in patients with dementia.[73] While two meta-analyses reported good efficacy, two Cochrane reviews reported little or no effectiveness, and increased side effects of antidepressants in patients with dementia.[73]
- The efficacy of SSRIs on anxiety in dementia is mixed: only two of seven RCTs reported citalopram, escitalopram, and other SSRIs possibly having some efficacy in reducing anxiety in Alzheimer's disease; the other five RCTs found no difference compared to placebo.[74]

Appetite loss and sleep disorders

While there were no studies evaluating the efficacy of antidepressants for loss of appetite, choice of antidepressant is based on exploiting known adverse effect profiles rather than primary antidepressant mechanisms – such as sedating properties for sleep disturbances or appetite-stimulating effects for loss of appetite, though evidence for these targeted applications remains limited.[71] The few studies on sleep disorders reported mixed efficacy for trazodone 50 mg over two weeks on total nocturnal sleep time, sleep efficiency, and time awake after sleep, with little to no effect on number of night-time awakenings or time asleep in the day.[75]

Harms associated with second-generation antidepressants

- Common SSRI adverse effects include nausea, dry mouth, headache, insomnia, weight change, anxiety, asthenia (daytime sedation associated with malaise, diminished mental energy, or emotional blunting), bleeding, coagulopathy, bone fractures, dizziness, extrapyramidal symptoms (e.g. akathisia, dystonia, parkinsonism), and hyponatraemia. The CitAD[e] trial reported that citalopram caused dose-dependent QT interval prolongation, which potentially may lead to a life-threatening cardiac arrhythmia, torsade de pointes (a form of polymorphic ventricular tachycardia).[76]
- Common mirtazapine adverse effects include drowsiness, weight gain, dry mouth, increased serum cholesterol, constipation, and increased appetite.[77]

Antipsychotics

Agitation

- Antipsychotics are mainly used for moderate or severe agitation (risk of harm to self or others), or aggression.[78]
- A Cochrane review reported that atypical antipsychotics (e.g. risperidone, olanzapine, aripiprazole, quetiapine) probably reduce agitation slightly (SMD -0.21, 95% CI -0.30 to -0.12) but probably have a negligible effect on psychosis (SMD -0.11, 95% CI -0.18 to -0.03).[79]
- Atypical antipsychotics increase the risk of somnolence and are probably also associated with slightly increased risk of extrapyramidal symptoms, serious adverse events, and death.[79]
- The combination of antipsychotics and AChE inhibitors commonly prescribed to patients with dementia for behavioural symptoms are associated with increased risks of major adverse cardiovascular and cerebrovascular events.[80] High-dose antipsychotics pose the greatest risk, requiring careful monitoring when used in this vulnerable population with multiple comorbidities.[81]

Antiepileptics

Agitation

- Generally very limited efficacy for reducing agitation (e.g. valproate),[82] but other agents (e.g. carbamazepine) may still be of benefit, though studies are limited by small size (unable to conduct pooled analyses) and mixed results (only one of four trials reported improvements in the Brief Psychiatric Rating Scale, measuring agitation, hostility, psychosis, and withdrawal or depression (Brief Psychiatric Rating Scale 1.13 points; 95% CI 0.54 to 1.73) relative to placebo.[78, 83]

Certainty of evidence	Values and preferences
The certainty of evidence overall for the efficacy of medication options range from very low- to high-certainty depending on the medication class and outcome studied (Appendix 2). Key limitations were lack of well-defined and relevant sample populations, use of non-validated scales for diagnosing or assessing specific BPSD in dementia,	Significant variability is expected in patients' and carers' values regarding pharmacotherapy for BPSD. Some carers may prioritise symptom relief and quality of life improvements, accepting medication risks, whilst others may prefer to minimise medication use and focus on non-pharmacological approaches. Patients' and carers'

[e] CitAD trial: Citalopram for agitation in Alzheimer's disease trial

methodological imprecision in blinding and allocation concealment, incorporation of studies with diverse designs, potentially introducing bias, absence of subgroup analysis (based on scale measurement scores), and small sample sizes in many studies, reducing statistical power.	preferences may be influenced by the severity and impact of specific BPSD symptoms, carer burden, previous experiences with medications, understanding of treatment goals and realistic expectations, and concerns about polypharmacy. Shared decision-making and individualised treatment management will accommodate these varying preferences.
Resources and feasibility	**Acceptability and other considerations**
AChE inhibitors and memantine are approved for Alzheimer's disease. Two antipsychotics, risperidone (indicated for persistent aggression in moderate and severe Alzheimer's disease) and brexpiprazole (indicated for persistent agitation associated with Alzheimer's disease) are approved for BPSD. Other medications are off-label. Antidepressants were suggested as an alternative to antipsychotics for BPSD, with the latter usually managed by specialists for high-risk cases who can harm themselves or others. This was supported by the Food and Drug Administration's 'black box' warning for antipsychotics due to concerns regarding the higher mortality rate observed in patients with dementia prescribed antipsychotics. Resource implications include the need for adequate consultation time to assess symptoms, discuss treatment options, monitor responses, and coordination with specialists when needed for complex cases or medications requiring specialist initiation. Some medications (antipsychotics, antiepileptics) are typically initiated in specialist settings.	The acceptability of pharmacotherapy for persistent BPSD may vary significantly among stakeholders: • Healthcare professionals agree on individualised approaches, though comfort levels may vary with different medication classes and off-label prescribing. • Patient and carers may show variable acceptance based on symptom severity, impact on daily functioning, previous experiences, support, and understanding of treatment rationale. Some view medication as necessary relief for distressing symptoms, whilst others may see it as 'chemical restraint' or abandoning non-pharmacological approaches. Factors affecting acceptance include clear communication about treatment goals and realistic expectations, transparent discussion of risks and benefits, involvement in shared decision-making, respect for patients', families', or carers' values, and ongoing support and monitoring arrangements.
Expert Group deliberation of above factors	
The Expert Group noted that the impact of BPSD is determined more by their effects on the patient's quality of life and the carer's stress, rather than the nature of the specific symptoms per se. As such, clear guidance on circumstances requiring specialist referral or emergency services is needed, and healthcare professionals should be empowered to initiate appropriate management strategies. The Expert Group emphasised the importance of considering carer burden in treatment decisions.	

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