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SPECIAL TOPIC SECTION

CCCDTD5 recommendations on the deprescribing of cognitive enhancers in dementia

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Abstract

Introduction: Cognitive enhancers (ie, cholinesterase inhibitors and memantine) can provide symptomatic benefit for some individuals with dementia; however, there are circumstances in which the risks of continuing treatment may potentially outweigh benefits. The decision to deprescribe cognitive enhancers must consider each patient's preferences, treatment indications, current clinical status and symptoms, prognosis, and dementia type.

Methods: The 5th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD5) established a subcommittee of experts to review current evidence on the deprescribing of cognitive enhancers. The questions answered by this group included: When should cognitive enhancers be deprescribed in persons with dementia and mild cognitive impairment? How should cognitive

enhancers be deprescribed? And, what clinical factors should be considered when deprescribing cognitive enhancers?

Results: Patient and care-partner preferences should be incorporated into all decisions to deprescribe cognitive enhancers. Cognitive enhancers should be discontinued in individuals without ongoing evidence of benefit or when the indication for cognitive enhancer use was inappropriate (eg, mild cognitive impairment). Deprescribing should occur gradually and cognitive enhancers should be reinitiated if patients' cognition or function deteriorates. Cognitive enhancers should be continued in individuals whose neuropsychiatric symptoms improve in response to treatment. Clinicians should not deprescribe cognitive enhancers in individuals with significant neuropsychiatric symptoms until symptoms have stabilized.

Conclusion: CCCDTD5 deprescribing recommendations provide evidence-informed recommendations related to cognitive enhancer deprescribing that will facilitate shared decision making among patients, care partners, and clinicians.

KEYWORDS
cholinesterase inhibitor, memantine, cognitive enhancer, dementia, deprescribing, discontinuation

1 | INTRODUCTION

Evidence for the effectiveness and safety of cognitive enhancers in dementia treatment is well established and the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD) has developed guidelines regarding the use of cognitive enhancers (ie, cholinesterase inhibitors [ChEIs] and memantine) in previous editions of the CCCDTD.[1,2] There has been increasing interest and evidence for use of cognitive enhancers in the management of severe dementia.[3–5] Similarly, considerations for the cessation of cognitive enhancers in individuals with advanced dementia[6] or end of life care, and in other situations, has become a topic of increasing interest. Efforts such as Choosing Wisely[7] and deprescribing initiatives[8] have identified the need to carefully examine the use of medications in frail older adults for whom the benefits of therapy may be uncertain or for which risks may outweigh benefits.[9]

In 2012, the 4th CCCDTD first identified recommendations for deprescribing of ChEIs.[1] These guidelines identified that discontinuation of ChEIs should be considered when there is unclear evidence of ongoing benefit, adverse events develop, or when an individual has end-stage dementia. Discontinuation of cognitive enhancers should be gradual and patients should be monitored for worsening of cognitive or neuropsychiatric symptoms that may necessitate restarting therapy (Table 1).

The purpose of the 5th CCCDTD guideline working group on the deprescribing of cognitive enhancers was to consider the previous recommendations from CCCDTD4[1] in light of new evidence related to deprescribing of cognitive enhancers. Our group also considered new topics related to discontinuation of cognitive enhancers that were not addressed in the previous CCCDTD recommendations.

2 | METHODS

2.1 | Selection of topics for guideline recommendations

A deprescribing subcommittee was created including experts in family practice and nursing home care, geriatric psychiatrists, geriatricians, and neurologists. We also sought to have representation from junior and senior clinicians and researchers as well as geographic representation from across Canada. A total of 13 individuals were included in this guideline recommendation group (Appendix A in supporting information).

2.2 | Search strategy

An initial search of published literature was conducted in April 2019 and updated in September 2020. The electronic databases MEDLINE, PsychINFO, the Cochrane Database of Systematic Reviews, and Google Scholar were searched using keywords for deprescribing (deprescribing, deprescriptions, discontinuation, cessation) AND cognitive enhancers (ChEIs, anti-cholinesterase, donepezil, galantamine, rivastigmine, memantine). Additional articles were obtained from reference lists provided by members of the deprescribing

recommendations working group along with reference lists of relevant articles identified through the preliminary search of the literature. The full details of the search strategy are provided in Appendix B in supporting information.

2.3 | Assessing strength of recommendations

Our guideline group used Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the certainty in evidence identified in our review and to provide strength of recommendations.[10] This process assesses the quality of evidence available for each recommendation, rating the quality of evidence as low (C), moderate (B), or high (A) depending on the underlying strength and consistency of evidence. Each recommendation is also provided with a strong (1) or weak (2) recommendation based on the evidence and balance of risks and benefits associated with each recommendation. A preliminary rating of recommendation strength was provided by the deprescribing guideline recommendation project leads (DS, NH) and consensus on the strength of recommendations was obtained through review and discussion among members of the deprescribing subcommittee.

2.4 | Guideline recommendation review process

An initial list of recommendations was drafted by the project leads (DS, NH) following review of existing guidelines and areas that required updated recommendations. This initial list of recommendations was then distributed to the full subcommittee for review and revision. One additional guideline recommendation was suggested after preliminary review of guideline recommendations by the deprescribing subcommittee (Recommendation 1). The subcommittee also provided strength of recommendation and quality of evidence assessments for each recommendation.

After consensus was reached by the subcommittee, the recommendations were voted on by the CCCDTD5 conference attendees. Online voting on the recommendations by the CCCDTD5 conference attendees occurred prior to the in-person meeting. Recommendations that achieved ≥80% endorsement during the online voting were accepted. Recommendations that received endorsement by >60% of the CCCDTD attendees but <80% endorsement were modified, discussed, and voted on again in person. Recommendations with <60% endorsement during online voting were excluded from the final recommendations. The final recommendations were published in a summary document along with the recommendations from the other CCCDTD5 subcommittees.[11]

3 | RESULTS

Our literature review identified one systematic review on the discontinuation of cognitive enhancers,[12] one randomized controlled trial (RCT) published after this review,[13] a systematic review of guideline recommendations for deprescribing of cognitive enhancers,[14] and a recent guideline on deprescribing of cognitive enhancers.[15] After reviewing the relevant research literature, our deprescribing recommendations subcommittee arrived at 10 recommendations related to deprescribing of cognitive enhancers (Table 2). We provided separate recommendations for ChEIs and memantine and recommendations relevant to different types of dementia. The recommendations and relevant evidence supporting each recommendation are provided in the subsequent sections of this guideline recommendations manuscript.

Recommendation 1: *Decisions related to deprescribing of cognitive enhancers should take into consideration the patient's preferences (for individuals who are capable of making treatment decisions), their prior expressed wishes (if these are known), and in collaboration with family or substitute decision makers for individuals who are incapable of providing informed consent.***(1C)**

RESEARCH IN CONTEXT

1. **Systematic Review**: We reviewed previous guidelines and existing systematic reviews to identify questions for guideline recommendation development. A strategy was executed in February 2019 using PubMed and additional electronic databases.
2. **Interpretation**: Our subcommittee provided guideline recommendations for clinicians to assist them in the deprescribing of cholinesterase inhibitors and memantine. We provide guidance on considerations for specific types of dementia and clinical considerations that are important to consider when making deprescribing decisions.
3. **Future Directions**: Research on how our guideline recommendations impact clinical practice and quality of life of persons living with dementia requires further study. Additional high-quality evidence is required around the risks and benefits of deprescribing of cognitive enhancers.

HIGHLIGHTS

- The decision to deprescribe cognitive enhancers should take into account patient and family member preferences.
- Cognitive enhancers should be deprescribed in individuals with dementia for whom benefits of therapy are unclear or for which risks of ongoing treatment outweigh benefits.
- The presence of neuropsychiatric symptoms needs to be considered in deprescribing decisions.
- Cognitive enhancers should be deprescribed in individuals with mild cognitive impairment.

TABLE 1 Recommendations from the CCCDTD4 on deprescribing of cholinesterase inhibitors*

Discontinuing ChEIs in patients with moderate to severe AD may lead to worsening of cognitive function and greater functional impairment as compared with continued therapy (Grade 2B). This risk must be balanced with the risk for known side effects and drug costs if therapy continues. It is suggested that ChEIs be discontinued when:

1. The patient and/or their proxy decision maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation;
2. The patient is sufficiently nonadherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem;
3. The patient's rate of cognitive, functional, and /or behavioral decline is greater or treatment compared with that prior to being treated;
4. The patient experiences intolerable side effects that are definitely or probably related to the ChEI;
5. The comorbidities of the patient make continued use of the agent either unacceptably risky or futile (eg, terminally ill); or
6. The patient's dementia progress to a stage (eg, Global Deterioration Scale stage
7. where there would be no clinically meaningful benefit from continued therapy.

When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, the suggestion is that the dose be tapered before stopping the agent and that the patient be monitored over the 1 to 3 months for evidence of an observable decline. If this decline occurs, it is suggested that consideration be given to reinstating therapy. (Grade 2C)

*From Herrmann et al. Alzheimer's Research & Therapy, 2013;5(Suppl 1):S5.
Abbreviation: CCCDTD4, 5th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; ChEI, cholinesterase inhibitors.

TABLE 2 Ten recommendations related to the deprescribing of cognitive enhancers

1. Decisions related to deprescribing of cognitive enhancers should take into consideration the patient's preferences (for individuals who are capable of making treatment decisions), their prior expressed wishes (if these are known), and in collaboration with family or substitute decision makers for individuals who are incapable of providing informed consent. (Strong recommendation, 1C)
2. For individuals taking a ChEI for AD, PDD, DLB, or VD for >12 months, discontinuation should be considered if: (a) there has been a clinically meaningful worsening of dementia as reflected in changes in cognition, functioning, or global assessment over the past 6 months in the absence of other medical conditions (eg, presence of delirium, significant concomitant medical illness) or environmental factors (eg, recent transition in residence) that may have contributed significantly to the observed decline; (b) no clinically meaningful benefit was observed at any time during treatment (improvement, stabilization, decreased rate of decline); (c) the individual has severe or end-stage dementia (dependence in most basic activities of daily living, inability to respond to environment or limited life expectancy); (d) development of intolerable side-effects (eg, severe nausea, vomiting, weight loss, anorexia, falls); (e) medication adherence is poor and precludes safe ongoing use of the medication or inability to assess the effectiveness of the medication. 1B (98%)
3. For individuals prescribed ChEIs for indications other than AD, PDD, DLB, or VD (eg, frontotemporal dementia, other neurodegenerative conditions), ChEI should be discontinued. 1B (93%).
4. For individuals taking memantine for AD, PDD, DLB, or VD for >12 months, discontinuation should be considered if: (a) there has been a clinically meaningful worsening of dementia as reflected in changes in cognition, functioning, or global assessment over the past 6 months in the absence of other medical conditions (eg, presence of delirium, significant concomitant medical illness) or environmental factors (eg, recent transition in residence) that may have contributed significantly to the observed decline; (b) no clinically meaningful benefit was observed at any time during treatment (improvement, stabilization, decreased rate of decline); (c) the individual has severe or end-stage dementia (dependence in most basic activities of daily living, inability to respond to environment or limited life expectancy); (d) development of intolerable side effects (eg, confusion, dizziness, falls); (e) medication adherence is poor and precludes safe ongoing use of the medication or inability to assess the effectiveness of the medication. 1C (96%)
5. For individuals prescribed memantine for indications other than AD, PDD, DLB, or VD (eg, frontotemporal dementia, other neurodegenerative conditions), memantine should be discontinued. 1C (91%)
6. Deprescribing of ChEIs or memantine should occur gradually and treatment reinitiated if the individual shows clinically meaningful worsening of cognition, functioning, neuropsychiatric symptoms, or global assessment that appears to be related to cessation of therapy. 1B (98%)
7. Dose reduction during deprescribing should follow general guidelines for deprescribing of medications with a reduction of dose by 50% every 4 weeks until the initial starting dose is obtained. After 4 weeks of treatment on the recommended starting dose, the cognitive enhancer could be discontinued. 2C (96%)
8. ChEIs should not be discontinued in individuals who currently have clinically meaningful psychotic symptoms, agitation, or aggression until these symptoms have stabilized unless these symptoms appear to have been worsened by the initiation of a ChEI or an increase in ChEI dose. 2B (78%, 100%)
9. Individuals who have had a clinically meaningful reduction in neuropsychiatric symptoms (eg, psychosis) with cognitive enhancers should continue to be treated with the cognitive enhancer even if there is evidence of cognitive and functional decline.
10. Cholinesterase inhibitors and memantine should be deprescribed for individuals with mild cognitive impairment. 1B (89%)

Abbreviations: AD, Alzheimer's disease; ChEI, cholinesterase inhibitor; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia; VD, vascular dementia.

Similar to the decision related to initiation of cognitive enhancers,[2] the process of deprescribing cognitive enhancers should take into account the wishes of persons living with dementia and their families and significant others.[6] Often the decision to discontinue cognitive enhancers will occur for individuals who have advanced dementia or who may be nearing end of life. In these circumstances the person living with dementia will most often lack capacity to make these decisions on their own and informed consent for discontinuing cognitive enhancers will be provided by a family member or other substitute decision maker. These discussions should include information about the potential risks and benefits of discontinuing treatment, a plan for monitoring response to discontinuation, and discussion about plans for reintroducing therapy if it is determined that deterioration in clinical status has occurred following discontinuation. It should be acknowledged that even when persons living with dementia have entered hospice services the decision to discontinue cognitive enhancers can be challenging for families.[16]

In many health regions, insurance coverage for cognitive enhancers is dependent on specific cognitive test scores or quantitative assessment of ongoing benefits of treatment.[17] These policies should be used to guide discussions of deprescribing of cognitive enhancers but not used solely in the decision to deprescribe as there may be clinical benefit in continuing cognitive enhancers in advanced dementia where cognitive test scores are below the cut-offs for ongoing insurance coverage.[6] In these circumstances discussions with the person living with dementia or family should also include information about the financial costs of continuing treatment with the cognitive enhancer.

Recommendation 2: *For individuals taking a ChEI for Alzheimer's disease (AD), Parkinson's disease dementia (PDD), Lewy body dementia (DLB), or vascular dementia (VD) for >12 months, discontinuation should be considered if*:

a. *there has been a clinically meaningful worsening of dementia as reflected in changes in cognition, functioning, or global assessment over the past 6 months in the absence of other medical conditions (eg, presence of delirium, significant concomitant medical illness) or environmental factors (eg, recent transition in residence) that may have contributed significantly to the observed decline;*
b. *no clinically meaningful benefit was observed at any time during treatment (improvement, stabilization, decreased rate of decline);*
c. *the individual has severe or end-stage dementia (dependence in most basic activities of daily living, inability to respond to environment or limited life expectancy);*
d. *development of intolerable side effects (eg, severe nausea, vomiting, weight loss, anorexia, falls); or*
e. *medication adherence is poor and precludes safe ongoing use of the medication or inability to assess the effectiveness of the medication.* **(1B)**

The discussion of deprescribing cognitive enhancers is characterized by the balancing of risks and benefits for an individual at that particular point in time. Cognitive enhancers have relatively consistent, although modest, evidence of benefits for individuals affected by AD,[4,18,19] mixed dementia, VD (or vascular cognitive impairment),[20] DLB,[21–23] and PDD.[22,24] At the present time, ChEIs remain the best supported pharmacological treatment for many common forms of dementia and their use should be discussed with persons who are diagnosed with these types of dementia as these medications can provide symptomatic benefits in cognition, functioning, and behaviors for many individuals.[18]

Discontinuation of ChEI therapy (either through deprescribing or patient non-adherence) is common in real-world settings. Up to 50% of individuals who are initially prescribed a ChEI discontinue within 1 year with up to 90% of individuals discontinuing over the course of 3 years.[17]

While ChEIs can provide temporary improvements in cognition, functioning, or behavior, a meaningful clinical deterioration for a period of 6 months should prompt a review of whether the ChEI should be deprescribed. In the absence of a clinical benefit observed following initiation of a ChEI, consideration should be given to deprescribing of treatment. In situations in which the individual's goals of care and quality of life are no longer focused on maintaining cognition and functioning, such as at the end of life, ongoing treatment with ChEIs may no longer align with these goals of care.

Intolerable side effects are uncommon during long-term treatment with ChEIs; however, the presence of symptoms known to be associated with their use may prompt deprescribing. These side effects tend to occur early in treatment when they do occur, but side effects can develop at any time during treatment. ChEIs are less likely to produce benefits, and more likely to contribute to side effects, when they are administered inconsistently and in the absence of medication adherence these medications should be discontinued.

Recommendation 3: *For individuals prescribed ChEIs for indications other than AD, PDD, DLB, or VD (eg, frontotemporal dementia, other neurodegenerative conditions), ChEIs should be discontinued.* **(1B)**.

As reviewed in Recommendation 2 of these guidelines and previous iterations of the CCCDTD, there is currently no evidence to support the use of ChEIs in other forms of dementia such as frontotemporal dementias,[25,26] dementias due to other neurological disorders,[27] or acquired forms of dementia. Given that there is limited evidence for any beneficial effects of ChEIs in these populations, and the potential for adverse effects associated with treatment, ChEIs are not recommended for the treatment of these types of dementia and they should be deprescribed in these situations in the absence of obvious benefits and in consultation with the patient and/or care giver.

Recommendation 4: *For individuals taking memantine for AD, PDD, DLB, or VD for >12 months, discontinuation should be considered if*:

a. *there has been a clinically meaningful worsening of dementia as reflected in changes in cognition, functioning, or global assessment over the past 6 months in the absence of other medical conditions (eg, presence of delirium, significant concomitant medical illness) or environmental*

factors (eg, recent transition in residence) that may have contributed significantly to the observed decline;

b. *no clinically meaningful benefit was observed at any time during treatment (improvement, stabilization, decreased rate of decline);*
c. *the individual has severe or end-stage dementia (dependence in most basic activities of daily living, inability to respond to environment, or limited life expectancy);*
d. *development of intolerable side effects (eg, confusion, dizziness, falls);*
e. *medication adherence is poor and precludes safe ongoing use of the medication or inability to assess the effectiveness of the medication.***(1C)**

Similar to Recommendation 2, Recommendation 4 provides clinical guidance related to deprescribing memantine. There is evidence supporting the use of memantine for AD,[28–30] VD, DLB,[23,31] and PDD[23] although the benefits of memantine for treating these types of dementia also tend to be modest. It should also be noted that much of the evidence for the use of memantine in dementia has been in the context of combination with a ChEI. As such, the benefit of continued treatment with memantine alone following discontinuation of the ChEI needs to also be considered.

We were unable to find any systematic reviews, and only a limited number of observational studies, investigating the discontinuation of memantine. One observational study of nursing home residents who were deprescribed memantine found that discontinuation of memantine was associated with a worsening of cognition and neuropsychiatric symptoms compared to ongoing treatment.[32] Our working group recommended that deprescribing of memantine be considered in clinical situations similar to those situations in which ChEIs are being considered for discontinuation although it should be noted that memantine tends to be associated with fewer side effects than ChEIs.[18] An ongoing study is evaluating the effects of deprescribing ChEIs with or without concomitant use of memantine.[33]

Recommendation 5. *For individuals prescribed memantine for indications other than AD, PDD, DLB, or VD (eg, frontotemporal dementia, other neurodegenerative conditions), memantine should be discontinued.* **(1C)**

Our working group was unable to find any consistent evidence to suggest that memantine is effective in the treatment of dementias other that those indicated in Recommendation 4. Therefore, it is recommended that memantine be deprescribed in individuals who are currently receiving treatment with memantine for conditions other than AD, VD, DLB, or PDD. This includes deprescribing in those with frontotemporal dementia[34] in the absence of obvious benefit and in consultation with the patient and/or care partner.

Recommendation 6: *Deprescribing of ChEIs or memantine should occur gradually and treatment reinitiated if the individual shows clinically meaningful worsening of cognition, functioning, neuropsychiatric symptoms, or global assessment that appears to be related to cessation of therapy*. (**1B**)

A systematic review of RCTs examining discontinuation of ChEIs identified five RCTs.[12] This meta-analysis identified that discontinuation of ChEIs can be associated with a worsening of cognition as measured on the Mini-Mental State Examination (standardized mean difference [SMD]: −0.29, 95% confidence interval [CI]: −0.45 to −0.13), worsening of neuropsychiatric symptoms (SMD on Neuropsychiatric Inventory: −0.32, 95% CI: −0.51 to −0.12, $P = 0.001$) and higher rates of trial dropouts (risk ratio = 1.33, $P = 0.002$). Most of the studies included in this review were conducted in community-based settings (eg, not in nursing homes) and most studies included individuals with mild to moderate severity of AD. Although deprescribing may be appropriate to consider, this meta-analysis would argue for careful monitoring and follow-up should a deprescribing decision be made. An RCT of ChEI discontinuation in nursing home residents with advanced dementia was published after this meta-analysis. This small trial found that there was no significant difference in the proportion of participants who experienced clinical worsening for the deprescribing group when compared to the continuation group.[35]

While many individuals with advanced dementia can have cognitive enhancers discontinued without worsening of clinical status, some individuals can have a worsening of cognition, function, or neuropsychiatric symptoms during deprescribing.[12] Most RCTs of deprescribing of ChEIs have used an abrupt approach to discontinuation without dose tapering.[12] It can be difficult to predict in advance which individuals are more likely to experience clinical deterioration following deprescribing of cognitive enhancers but some features such as the presence of neuropsychiatric symptoms have been associated with an increased risk of clinical deterioration following deprescribing.[35]

Therefore, it is recommended that cognitive enhancers be gradually reduced over time and if clinical deterioration occurs during discontinuation that appears to be related to dose reduction or cessation of therapy then the cognitive enhancer should be reinstituted.[15] The cognitive enhancer may be considered for deprescribing at another time in the future when a process of gradual dose reduction and observation can be attempted. In situations in which cognitive enhancers are deprescribed due to intolerable side effects or poor adherence the cognitive enhancer should be discontinued unless measures have been put in place to correct these factors.

Recommendation 7: *Dose reduction during deprescribing should follow general guidelines for deprescribing of medications with a reduction of dose by 50% every 4 weeks until the initial starting dose is obtained. After 4 weeks of treatment on the recommended starting dose, the cognitive enhancer could be discontinued.* (**2C**)

Once a decision to deprescribe cognitive enhancers has been made the process for discontinuation should be gradual unless the cognitive enhancer needs to be deprescribed abruptly due to side effects or immediate safety concerns exist related to continued use of the medication. While there are no known risks of developing severe physiological symptoms related to the withdrawal of cognitive enhancers, it is generally recommended in deprescribing guidelines that the dose of medications be reduced gradually over time to minimize the potential risks of developing symptoms related to cessation of therapy.[8,14,15] A gradual reduction in dosage also allows persons with dementia, their families, and clinicians to closely monitor for the worsening of symptoms early in the deprescribing process. Early identification of changes in behavior or function may help avoid unnecessary deterioration in clinical status or the initiation of other treatments or investigations that may be more harmful than continued treatment with a cognitive

enhancer. Identification of clinical deterioration associated with deprescribing may then allow clinicians to either temporarily pause further deprescribing or reinstitute treatment if deterioration has been noted.

Recommendation 8: *ChEIs should not be discontinued in individuals who currently have clinically meaningful psychotic symptoms, agitation, or aggression until these symptoms have stabilized unless these symptoms appear to have been worsened by the initiation of a ChEI or an increase in ChEI dose.* (**2B**)

Discussions related to the deprescribing of cognitive enhancers frequently occur when individuals have advanced dementia. Neuropsychiatric symptoms such as psychosis, agitation, and aggression are common in this population and are often the main focus of clinical management. There is limited evidence that initiation of treatment with cognitive enhancers is beneficial for reducing symptoms of agitation and aggression in AD,[36,37] although recent evidence from an observational study found that treatment with ChEIs reduced the risk of antipsychotic and anxiolytic initiation.[38] However, in AD, both ChEIs[39,40] and memantine[30,40] are associated with modest improvements in overall neuropsychiatric symptoms. At the same time, on average a small worsening of neuropsychiatric symptoms has been observed during discontinuation of ChEIs.[12] Therefore, for individuals who have significant neuropsychiatric symptoms it was recommended that initiation of deprescribing be delayed until these behavioral symptoms have stabilized. Clinicians should also monitor for emergence of neuropsychiatric symptoms in the 3 to 6 months following deprescribing for the potential worsening of these symptoms associated with cessation of cognitive enhancers. There is also evidence that the presence of some neuropsychiatric symptoms such as hallucinations and delusions may predict poor response to deprescribing of cognitive enhancers,[35] highlighting the importance of being cautious of deprescribing cognitive enhancers in individuals with significant neuropsychiatric symptoms.

Recommendation 9: *Individuals who have had a clinically meaningful reduction in neuropsychiatric symptoms (eg, psychosis) with cognitive enhancers should continue to be treated with the cognitive enhancers even if there is evidence of cognitive and functional decline* **(2B)**.

Cognitive enhancers have received regulatory approvals for treating dementia based primarily on treatment benefits observed on outcomes measuring cognition, functioning, and clinical global impression. However, some individuals may have limited cognitive or functional response to treatment but have clinically significant improvement in neuropsychiatric symptoms.[18,30,39] For some types of dementia like DLB and PDD,[23,24] cognitive enhancers can be associated with reductions in neuropsychiatric symptoms such as psychosis, and the risks associated with alternative medications such as antipsychotics can be particularly problematic. For these reasons, if an individual has had a significant improvement in neuropsychiatric symptoms during treatment with a cognitive enhancer, consideration should be given to continuing treatment, even if the benefits on cognition or functioning have been marginal. In these circumstances, insurance providers may not provide ongoing insurance coverage for treatment with the cognitive enhancer and discussions with the person with dementia and their family members may need to occur to determine ability to pay for ongoing treatment in this context.

Recommendation 10: *ChEIs and memantine should be deprescribed for individuals with mild cognitive impairment.* **(1B)**

There is no evidence that cognitive enhancers are associated with improvements in cognition or function in mild cognitive impairment (MCI or mild neurocognitive disorder in Diagnostic and Statistical Manual of Mental Disorders 5th Edition [DSM5] terminology).[41–43] Cognitive enhancers are associated with adverse effects in individuals with MCI.[43] Individuals that have been prescribed cognitive enhancers should have their cognitive enhancer deprescribed due to the lack of evidence for benefit and the potential for side effects. Whether individuals with MCI who also have biomarker evidence to suggest early development of AD or other types of dementia benefit from treatment with cognitive enhancers requires further study.

4 | CONCLUSION

Deprescribing of cognitive enhancers in individuals with dementia is an important and challenging clinical issue. Our guideline recommendations will facilitate shared decision making among patients, care partners, and clinicians related to cognitive enhancer deprescribing, specifically, the risks and benefits of deprescribing in individual cases. While the underlying evidence used to generate our recommendations is relatively strong and consistent in some areas related to deprescribing of cognitive enhancers, additional research is required to better understand the risks and benefits of cognitive enhancer deprescribing and potential treatment alternatives.

CONFLICTS OF INTEREST

Dr. Herrmann: no conflicts to report; Dr. Ismail: consulting fees from Janssen, Lundbeck and Otsuka, outside the submitted work; Dr. Collins: no conflicts to report; Dr. Desmarais: no conflicts to report; Dr. Goodarzi: no conflicts to report; Dr. Henri-Bhargava: no conflicts to report; Dr. Iaboni: no conflicts to report; Dr. Kirkham: no conflicts to report; Dr. Massoud: speaker's honoraria from Pfizer and Astellas in the last two years, outside the submitted work; Dr. Moser: no conflicts to report; Dr. Silvius: no conflicts to report; Dr. Watt: no conflicts to report; Dr. Seitz: participation in clinical trials sponsored by Hoffmann La Roche, outside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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