A GUIDE TO

deprescribing

phn TASMANIA
An Australian Government Initiative

primary health TASMANIA

CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

CHOLINESTERASE INHIBITORS

KEY POINTS

- **Studies have demonstrated statistically significant differences between cholinesterase inhibitors and placebo in terms of cognitive, behavioural, functional and global assessments. However, the magnitude of the differences are modest and it is unclear whether these would translate into changes that would improve the person in terms of their daily care and supervision requirements.**
- **Patients who have major changes in their life circumstances, such as significant deterioration of health or nursing home placement, should have their cholinesterase inhibitor use reviewed.**
- **Patients who have serious side effects consistent with use of cholinesterase inhibitors should trial cessation of the agent.**
- **Individualised decisions about discontinuing cholinesterase inhibitors should be made rather than being based on single factors such as MMSE score.**
- **It is unclear whether cessation of a cholinesterase inhibitor results in a clinically significant decline in cognition or other dementia symptoms.**

FOR BETTER HEALTH OUTCOMES

CONTEXT

This guide considers the use of cholinesterase inhibitors to improve cognitive function in people with Alzheimer's disease.

RECOMMENDED DEPRESCRIBING STRATEGY

- Australian guidelines recommend that if discontinuation is to be considered, this should be undertaken as an initial trial with close periodic monitoring for discontinuation syndromes or a decline in the symptoms of dementia.
- A trial of deprescribing may be considered in a person with Alzheimer's disease, DLB, Parkinson's disease dementia, vascular dementia or mixed dementia who has used the medication for 12 months or more. If a person taking a cholinesterase inhibitor does not have one of these types of dementia then a trial of deprescribing may commence irrespective of the duration of cholinesterase inhibitor treatment.
- The dose of the cholinesterase inhibitor should preferentially be tapered gradually rather than ceased immediately. A suitable tapering regimen may involve halving the dose every four weeks until the lowest possible dose is reached, then maintaining this dose for a further four weeks before cessation. If there is a more urgent need to cease a cholinesterase inhibitor then there is little evidence to suggest that abrupt cessation increases the risk of withdrawal symptoms.
- Close monitoring of the person for a decline in their condition should be undertaken periodically throughout the withdrawal process. The cholinesterase inhibitor may be reinitiated if there is evidence of the person's condition deteriorating.
- A 2018 clinical practice guidelines on deprescribing cholinesterase inhibitors is shown on **page 5**.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits › Slowing of cognitive decline associated with Alzheimer's Dementia	**Increased Benefit** › Presence of mild or moderate Alzheimer's Dementia › A good initial response to starting doses of cholinesterase inhibitors › Functionally able to live in non-residential care	**Decreased Benefits** › Severe Alzheimer's Dementia › Significant vascular disease (either microvascular or macrovascular morbidity) › Limited life expectancy
Main Harms › Gastrointestinal upset, urinary incontinence, asthma, bradycardia	**Reduced Harms** › Functionally independent and robust physical condition	**Increased Harms** › Presence of Asthma, Urinary Incontinence, Bradycardia or Gastrointestinal disorders › Low body weight › Frailty

BACKGROUND

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are prescribed to improve cognitive function in people with certain forms of dementia, including Alzheimer's disease, vascular dementia and dementia with Lewy bodies (DLB). As at June 2018, all three agents are only licenced in Australia for the treatment of Alzheimer's disease, a condition expected to approximately triple in prevalence over the next 40 years. Approximately 30% of Australians over the age of 85 have dementia, over 50% of residents in permanent residential care are diagnosed with dementia.[1]

EFFICACY

By inhibiting the synaptic metabolism of acetylcholine, reversible cholinesterase inhibitors enhance cortical cholinergic neurotransmission, intended to improve cognition and delay the effects of Alzheimer's disease.[2]

The efficacy of the cholinesterase inhibitors was reviewed and analysed by Tan et al in 2014.[3] They broadened the spectrum of outcome measures and sought to determine whether there were benefits in cognitive, behavioural or functional impairment in different stages of severity of Alzheimer's disease. They limited their analysis to randomised, double blinded, placebo controlled studies.

COGNITIVE FUNCTION

Tan et al reviewed 12 studies of cholinesterase inhibitors (donepezil 6 studies, galantamine 3 studies, rivastigmine 3 studies). All studies evaluated patients with mild to moderate dementia with a mean age of ~74 years. Two-thirds of the participants were female. All trials used the Alzheimer's disease Assessment Scale-Cognition (ADAS-COG) to assess cognitive outcomes over 24-26 weeks and baseline mini mental state examination (MMSE) varied from 16-24. A change in the ADAS-COG of 4 units or more is considered clinically relevant in terms of significant improvement or deterioration in cognition.

Cognitive effects were statistically significant for all drugs with a pooled weighted mean difference of -1.29 points (95% CI -2.30 to -0.28). There were no clear differences between the three cholinesterase inhibitors with differences in ADAS-COG as shown below:

- Donepezil 5mg: -1.95 (95% CI -2.60 to – 1.29)
- Donepezil 10mg: -2.48 (95% CI -3.23 to – 1.73)
- Rivastigmine: -2.01 (95% CI -2.69 to – 1.32)
- Galantamine 24mg: -3.03 (95% CI -3.66 to – 2.41)
- Galantamine 32mg: -3.20 (95% CI -3.28 to – 3.12)

In people with more severe Alzheimer's disease (MMSE <10), four studies of cholinesterase inhibitors are available (donepezil 4 studies [4,5,6,7] galantamine 1 study[8]). All of these studies had patients with advanced disease (MMSE 6-9). The Severe Impairment Battery (SIB) was used to evaluate cognitive benefit. The SIB scale (maximum score 100) scores for participating patients were in the 50-70 range and improvements were shown over 6 months of ~5 points on this scale. There were widely variable benefits with large standard deviations around the differences. In addition, the slight improvement in cognitive function often failed to improve overall activities of daily living. [4,5,6,8]

Other types of dementia may respond differently to cholinesterase inhibitors. There is no benefit shown for the use of these agents in fronto-temporal dementia, but there is a theoretical role for cholinesterase inhibitors in patients with dementia associated with Lewy Bodies and also in dementia associated with Parkinson's disease.

In a systematic review of cholinesterase inhibitors for Parkinson's disease,[9] there was a slowing of cognitive decline in four studies. This was determined by a difference in MMSE of 1.12 units (95% CI 0.61 to 1.64) over a period of 10-24 weeks from a starting MMSE of 19-27.[9] The impact of cholinesterase inhibitors for Lewy Body Disorders was reviewed by Matsunaga et al in 2015. [10] They identified 16 studies (11 donepezil, 2 galantamine, 3 rivastigmine) and the compounded mean difference in MMSE over a mean duration of 13 weeks was 0.53 points (95%CI 0.35-0.72), with rivastigmine and donepezil being more effective than galantamine.[10]

BEHAVIOURAL SYMPTOMS

The meta-analysis by Tan et al included 6 cholinesterase inhibitor studies (donepezil 3, rivastigmine 1, galantamine 2) that used the Neuropsychiatric Inventory (NPI) to score behavioural outcomes in people with Alzheimer's disease. They found that donepezil 10mg daily reduced NPI by 2.72 points (95%CI 0.52 to 4.92) over 24 weeks, galantamine 24mg daily reduced NPI by 1.72 points (95%CI 0.33-3.12), but that rivastigmine 12mg orally did not change the NPI. [3] To put these changes into perspective, a change of 11 NPI points (from a baseline of ~37) was achieved for risperidone over 12 weeks in the CATIE-AD trial which was primarily responsible for approval of risperidone for management of behavioural and psychological symptoms of dementia.[11]

In Matsunaga et al's meta-analysis of cholinesterase inhibitor use in DLB,10 NPI was reduced by a mean of 0.28 points (95%CI 0.03-0.53) across all 16 studies, again with donepezil and rivastigmine being more effective than galantamine.[10]

FUNCTIONAL OUTCOME

Functional outcomes are most commonly measured using the Alzheimer's disease Co-operative Study – Activities of Daily Living Inventory (ADCS-ADL) scoring system (maximum score=78). In the Tan meta-analysis,[3] seven studies used mean change in ADCS-ADL (from baselines of 14-52) to assess functional outcomes (3 donepezil,[4,5,6] 3 galantamine [8,12,13] and 1 rivastigmine[14]). Donepezil 5mg daily did not change the score but donepezil 10mg improved the score by 1.03 units, galantamine by 0.68 units and rivastigmine by 1.8 units.[3]

GLOBAL ASSESSMENT

The majority of studies that assess overall benefit utilise the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) tool. This has a seven-point outcome from very much improved, much improved, minimally improved through no change to minimal worsening, moderate worsening and marked worsening. Studies commonly amalgamate all improvements and worsening/no change together to form a dichotomous variable (improved vs not improved/worsened) for analysis.

In the Tan meta-analysis,[3] 10 studies addressed the global benefit of cholinesterase inhibitors for Alzheimer's Dementia using the CIBIS-Plus as a measure (5 donepezil,[5,6,15,16,17] three galantamine,[12,13,18] two rivastigmine[19,20]). Each of the agents had a higher likelihood of improvement of CIBIS-Plus score compared to placebo (donepezil 5mg -Odds Ratio 1.55, donepezil 10mg -Odds Ratio 1.66, Galantamine 24mg -Odds Ratio 1.18, Galantamine 32mg- Odds Ratio 1.49, rivastigmine- Odds Ratio 1.72). **Improvement in scores occurred in 23-34% of patients receiving a cholinesterase inhibitor, compared to 15-29% in patients receiving placebo.** Absolute increases in improvement rates varied from 5 to 14% (NNT 7-20).

Only some of the studies presented information from the seven point CIBIS-plus scale. In those studies, **the majority of the improvement was rated as minimal, with less than 10% of subjects having much or very much improved ratings**.[5,12,16,17]

DELAY IN NURSING HOME ADMISSION

There is some evidence that use of cholinesterase inhibitors may delay admission to nursing home. An initial observational study in the USA evaluated time to nursing home admission and mortality in 387 people with probable Alzheimer's disease (MMSE ~18, mean age ~72years) treated with cholinesterase inhibitors, compared to 416 people who did not take any treatment.[23] They found no association of medication use with mortality, but found that cholinesterase inhibitors delayed nursing home admission by several years. However, this was not a randomised study, and people who were taking cholinesterase inhibitors had higher MMSE results, a higher level of education, better scores for activities of daily living and were less likely to be taking antipsychotic agents.[23]

In a secondary analysis of the DOMINO-AD trial, a [24] proportion of people were randomised to continue (n=73) or cease (n=73) donepezil, following approximately 12 months of previous treatment with donepezil. After four years, 36 (49%) people taking donepezil had been admitted to a nursing home, while 42 (58%) of the people who had ceased donepezil had been admitted. The 25th percentile time of admission for the continuation group was 12.7 months and that for the discontinuation group was 8.9 months (difference of 3.8 months- 95% CI 1.5 to 7 months). There was no difference in the median time for nursing home admission and no difference at the end of four years. The authors concluded that withdrawal of donepezil in people with moderate to severe Alzheimer's disease increased the risk of nursing home placement in the first 12 months, but made no difference in the following three years (or over the entire 4 year period).[24] The longer term admission rate is likely to be a more reliable estimate of delay to nursing home admission time.

OTHER EFFECTS

There is some evidence associating cholinesterase use in dementia with beneficial cardiovascular outcomes and reduced mortality. A 2018 systematic review and meta-analysis of 31 studies found that there was a significantly lower risk of cardiovascular events (defined as stroke, acute coronary syndrome and cardiovascular mortality) in people taking cholinesterase inhibitors (hazard ratio 0.63, 95% confidence internal 0.45 to 0.88). However, these data are based on cohort and longitudinal studies, and it cannot be inferred that cholinesterase inhibitor use alone was responsible for these benefits. [21]

SUMMARY OF EFFICACY AND GUIDELINES FOR USE

The studies discussed above have demonstrated statistically significant differences between cholinesterase inhibitors and placebo in terms of cognitive, behavioural, functional and global assessments. However, the magnitude of the differences are modest and it is unclear whether these would translate into changes that would improve the person in terms of their daily care and supervision requirements.

Amidst this summary data there appear to be patient groups who derive greater benefit from cholinesterase inhibitor therapy (responders) and those who do not (non-responders). Unfortunately, there do not appear to be reliable clinical indicators to guide whether an individual taking such therapy is likely to be a "responder" or a "non-responder". [22]

It is worth clarifying that cholinesterase inhibitors do not alter the underlying neurodegenerative process. The trials are also all of relatively short duration, and it is also unclear whether long term therapy with cholinesterase inhibitors continues to have even a modest benefit after 12 months of treatment.

Australian clinical practice guidelines for dementia in Australia support the use of cholinesterase inhibitors for symptomatic treatment of Alzheimer's disease. [25] They recommend any one of the available cholinesterase inhibitors should be considered as options for managing the symptoms of mild-to-moderate Alzheimer's disease and state that their use "could be considered" in severe Alzheimer's disease.[25] These guidelines also suggest considering any of the cholinesterase inhibitors for symptomatic treatment of DLB, Parkinson's disease dementia, vascular dementia or mixed dementia.

It should be noted that the current Pharmaceutical Benefits Scheme (PBS) in Australia only subsidises the initial use of cholinesterase inhibitors for mild to moderately severe Alzheimer's disease (MMSE 10-24), not for other forms of dementia, and also does not subsidise dual therapy (with memantine and a cholinesterase inhibitor). [26]

Guidelines from the United Kingdom are more specific regarding the choice of cholinesterase inhibitors and dementia types. The British Association for Psychopharmacology consensus statement regarding anti-dementia drugs in clinical practice recommend that any cholinesterase inhibitor may be used in mild to severe Alzheimer's disease, but only rivastigmine or donepezil in DLB or dementia associated with Parkinson's disease. [27] In contrast to the Australian guidelines, neither this group nor the 2018 NICE Guidelines recommend cholinesterase inhibitors be used for vascular dementia, unless it is suspected that suspected that Alzheimer's disease, Parkinson's disease dementia or DLB is also present. [28]

DISCONTINUATION SYNDROMES

There are case reports of people experiencing withdrawal symptoms after stopping cholinesterase inhibitors.[39,40] The symptoms reported consisted of significant anxiety and worsening of dementia symptoms, including hallucinations and delusions. In many of these cases, reintroduction of the cholinesterase inhibitor resulted in improvement in these withdrawal symptoms.

There are some randomised studies of cholinesterase inhibitor discontinuation that may support the notion that worsening dementia symptoms may be a direct result of therapy cessation. Scarpini et al randomised people to either continue galantamine or change to a placebo after having taken galantamine for 12 months.[41] There were no differences in the number of people who had a decline in the ADAS-Cog of 4 points or more and no difference in the global assessment (using CIBIC-Plus).[41] In the DOMINO-AD trial,[42] people with moderate to severe Alzheimer's disease (MMSE 5-13) were randomised to continue or cease donepezil after 12 months of previous treatment. After 12 months, people who continued donepezil had a MMSE score on average 1.9 points higher (95% CI 0.7 to 3.1) and an improved ADL score of 3.9 points on a 60 point scale (95%CI 0.1 to 5.6).[42]

A study of 40 people showed no difference in MMSE after cessation of cholinesterase inhibitors in institutionalised people.[43] However, this study found that the presence of hallucinations and delusions potentially predicted clinical deterioration following cessation of the cholinesterase inhibitor. This is despite a meta-analysis review of these and two other studies that concluded that the net reduction in MMSE was clinically insignificant (0.29 points, 95%CI 0.13 to 0.45). [44]

These studies largely examined the effects of discontinuing a cholinesterase inhibitor in people who had been previous responders to therapy. As such, cessation may result in a reduction in previously achieved benefit.

ADVERSE EFFECTS

Acetylcholine is involved in a range of central and peripheral nervous system functions, and as such, inhibition of its catabolism (by inhibition of cholinesterase) can result in a range of undesirable adverse effects. The most frequent adverse effect associated with the cholinesterase inhibitors used for dementia involve the gastrointestinal system. Common symptoms include nausea, vomiting and diarrhoea, and these symptoms tend to be most marked during the initiation of therapy or with dose escalation. Urinary frequency and precipitation of, or worsening of urinary incontinence are also commonly encountered side effects.

The commonly encountered side effects are shown in **Table 1** below:

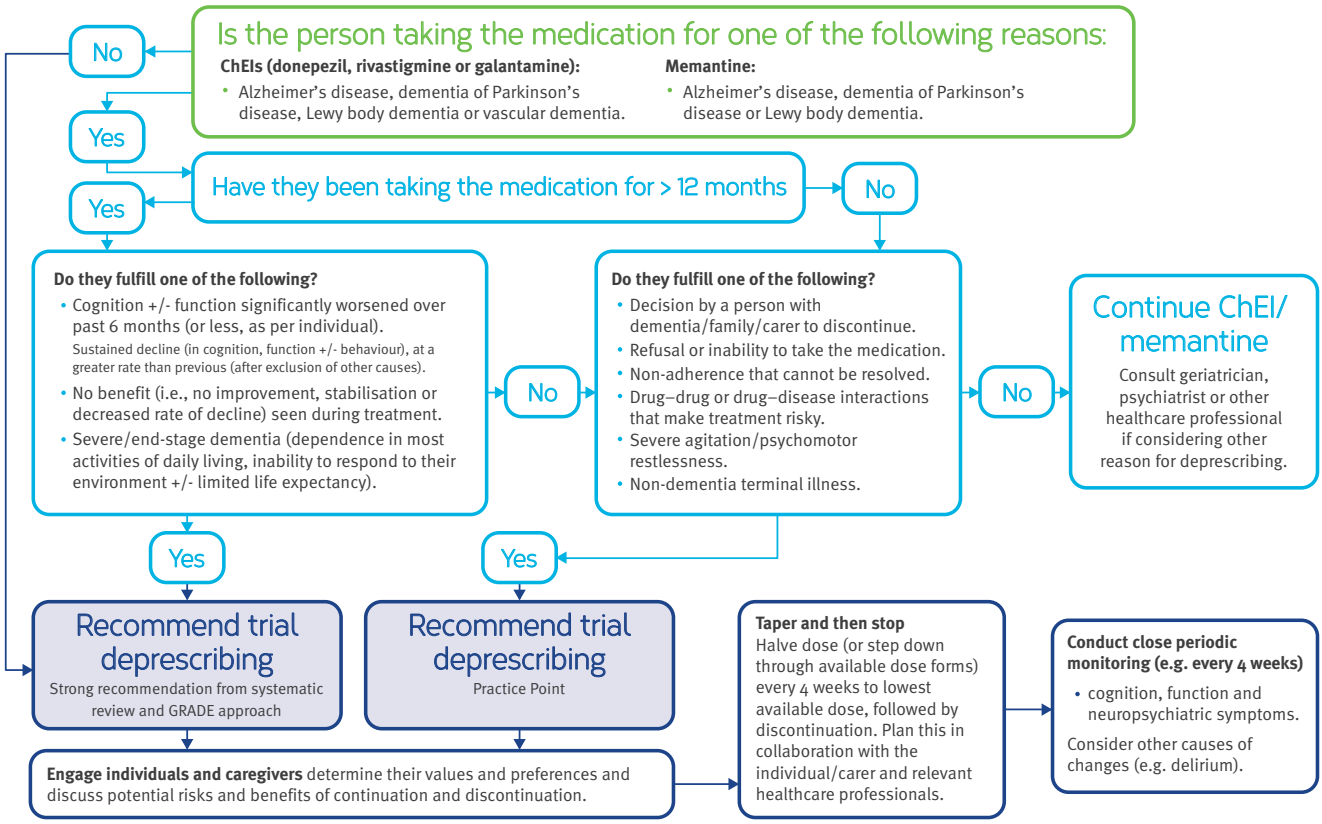
CATEGORY OF REACTION	COMMON SYMPTOMS/SIGNS
Nervous system disorders	syncope, loss of consciousness, dizziness, convulsions, dyskinesias and movement disorders
Psychiatric disorders	confusion and disorientation, hallucinations, anxiety, aggression
Gastrointestinal disorders	nausea and vomiting, diarrhoea
Cardiac disorders	bradycardia, AV block, cardiac arrest
Skin and subcutaneous tissue disorders	rashes, pruritis (transdermal patches only)
Respiratory, thoracic, and mediastinal disorders	dyspnoea, bronchospasm
Renal and urinary disorders	urinary incontinence or retention

Table 1: Common adverse effects to cholinesterase inhibitors

A number of other rare, but often serious adverse effects are possible. There have been several reports to the Advisory Committee on the Safety of Medicines (ASCOM) of bradycardia, syncope, myocardial infarction and AV block for all three available cholinesterase inhibitors.[29, 30] Analysis of pharmacovigilance databases in the USA and Canada, [31,32] and of the Vigibase worldwide adverse drug reactions database[33] support cardiac disorders and gastrointestinal disorders as frequently reported adverse effects.

More recently, an analysis of Australian PBS data associated cholinesterase inhibitor initiation with the subsequent commencement of new medications for seizures, anxiety, insomnia, nausea, and diarrhoea. [34]

DEPRESCRIBING ALGORITHM [35]



Monitoring during tapering and after discontinuation

Timing of symptoms after dose reduction/ discontinuation	Types of symptoms	Action to be taken by family/nurses/ care staff	Possible cause*
Less than 1 week	Severe symptoms, including agitation, aggression, hallucina-tions or reduced consciousness	Restart previous dose immediately and contact responsible healthcare professional as soon as possible	Adverse drug withdrawal reaction
2 to 6 weeks	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible healthcare professional and consider restarting previous dose and/or make an appointment to see responsible healthcare professional at the next available time	Re-emergence of symptoms that were being treated by ChEI/ memantine
6 weeks to 3 months	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible healthcare professional at the next available time to make an appointment	Likely progression of condition or possible re-emergence of symptoms that were being treated by ChEI/memantine
› 3 months	Any	As per usual care	Progression of condition

- *Exclude other causes of change in condition (e.g. infection or dehydration) first.
- Discuss monitoring plan with the individual/family/carer and write it down for them (e.g. frequency and type of follow-up). Ensure they have a way to contact a clinician if needed.

Engaging individuals and family/carers

Determining suitability for deprescribing

- Discuss treatment goals – what do they value the most (cognition, quality of life, remaining independent)?
- Ask about experience with dementia symptoms when treatment started and over last 6 months.
- Ask about side effects.

Helping the individual and family/carers to make an informed decision

- Deprescribing is a trial — medication can be restarted if appropriate.
- There are uncertain benefits and harms to both continuing and discontinuing the medication.
- Tailor discussion about benefits and harms to the individual.
- Explore fears and concerns about deprescribing.
- Consider medication costs and local reimbursement/subsidisation criteria.
- If the recommendation to deprescribe is being made due to progression of dementia, remind family/ carers that the person with dementia may continue to decline after deprescribing, and explain why.

Non-pharmacological management and ongoing care after deprescribing

See (http://sydney.edu.au/medicine/cdpc/resources/dementia-guidelines.php) for Australian guidelines on care of people with dementia, including behavioural and psychological symptoms.

ChEI and memantine availability (Australia)

Drug	Strength
Donepezil (Aricept®, Aridon®, Arazil®)	Tablet – 5mg, 10mg
Galantamine (Galantyl®, Gamine XR®, Reminyl®)	Controlled release capsule – 8mg, 16mg, 24mg
Rivastigmine (Exelon®)	Capsule – 1.5mg, 3mg, 4.5mg, 6mg
	Patch – 4.6mg/24 hours, 9.5mg/24 hours, 13.3mg/24 hours
Memantine (Ebixa®, Memanxa®)	Tablet – 10mg, 20mg

ChEI and memantine side effects

- Common: include gastrointestinal effects, dizziness, confusion, headache, insomnia, agitation, weight loss and falls.
- Rare (ChEI): may include urinary, cardiovascular (e.g. bradycardia), pulmonary and dermatological (e.g. Stevens-Johnson syndrome) complications, Pisa syndrome, seizures, gastrointestinal haemorrhage and rhabdomyolysis.
- Lack of evidence of potential harms in complex older adults.

Reeve E, Farrell B, Thompson W, at al Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine. 2018.
ISBN-13: 978-0-6482658-0-1 Available from: http://sydney.edu.au/medicine/cdpc/resources/deprescribing-guidelines.php

deprescribing.org Bruyère Research Institute Cognitive Decline Partnership Centre The University of Sydney

FACTORS TO CONSIDER

Several publications that provide guidance on deprescribing cholinesterase inhibitors have been released,[35,36] including an Australian-lead 2018 clinical practice guideline that specifically addresses this topic. However, the evidence regarding deprescribing of cholinesterase inhibitors is currently limited and of low quality, and no large, well-designed, long-term studies have been undertaken. There is currently minimal high-quality evidence of the effects of cholinesterase use beyond 12 months of treatment. Consequently, deprescribing recommendations are generally consensus-based, rather than evidence based.

The main factors to consider in relation to cholinesterase use are the level of clinically meaningful response achieved and any adverse effects that may be present.

Clinically meaningful response to treatment may be demonstrated in areas such as the following:

- the person's quality of life, including (but not limited to) level of independence and happiness;
- the person's cognitive function, including (but not limited to) memory, recognition and engagement with the environment; and
- the person's behavioural symptoms, including (but not limited to) hallucinations, delusions, anxiety, marked agitation or associated aggressive behaviour.

Amongst practitioners, there is a general reluctance to rely on any single measure of cognition, function and/or behaviour (in particular the MMSE) as a guide to efficacy, or to aid in deprescribing decisions.[37] It is inappropriate to arbitrarily cease cholinesterase inhibitors in people with Alzheimer's disease due to disease severity alone. [38]

IN FAVOUR OF DEPRESCRIBING

- At any time during treatment, the presence of adverse effects that impact on quality of life and clinical symptoms should prompt a review of the ongoing need for the agent.
- People who are taking cholinesterase inhibitors for indications other than Alzheimer's disease, DLB, Parkinson's disease dementia, vascular dementia or mixed dementia should be considered for a trial discontinuation of the cholinesterase inhibitor.
- People who have had a trial of therapy (as per the PBS) and have not demonstrated a clinically meaningful response may be considered for discontinuation of the cholinesterase inhibitor.
- People who have a major change in life circumstances such as admission to residential care should have their use of cholinesterase inhibitors reassessed. Other triggers may include significant deterioration in cognition and/ or function. In such cases, benefit from cholinesterase inhibitors may no longer be relevant to the main symptoms of concern.

AGAINST DEPRESCRIBING

- People who demonstrate ongoing, meaningful clinical benefit (functionally and/or cognitively stable) should continue on the medication with ongoing monitoring for continued benefit or the development of any adverse effects.
- People dwelling in the community (as opposed to in residential care) with adequate functional capacity (in terms of activities of daily living or similar) and appropriate support mechanisms may continue to derive benefit and may have a delay in nursing home admission.
- People who clearly clinically deteriorate after cessation of a cholinesterase inhibitor may benefit from reintroduction of the agent.

REFERENCES

1. Brown L, Hansnata E, La HA. Economic cost of dementia in Australia 2016-2056. Canberra, Australian Capital Territory: National Centre for Social and Economic Modelling, Institute for Governance and Policy Analysis, University of Canberra;2017.
2. Schwarz S, Froelich L, Burns A. Pharmacological treatment of dementia. Curr Opin Psychiatr 2012; 25(6): 542-550.
3. Tan CC, et al Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's Disease: A systematic review and meta-analysis. J Alz Dis 2014; 41: 615-631.
4. Winblad B, et al Severe Alzheimer's Disease Study Group. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet. 2006 Apr 1;367(9516):1057-65.
5. Homma A, et al Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24 week, double blind, placebo-controlled, randomized trial. Dementia Geriatr Cogn Disord 2008; 25: 399-407.
6. Black SE, et al Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology 2007; 69: 459-469.
7. Jia J, et al Efficacy and safety of donepezil in Chinese patients with severe Alzheimer's disease: a randomized controlled Trial. Journal of Alzheimer's disease: JAD. 2017;56(4):1495-504.
8. Burns A, et al Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. Lancet Neurol. 2009 Jan;8(1):39-47.
9. Pagano G, et al Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatr 2015; 86: 767-773.
10. Matsunaga S, Kishi T, Yasue I, Iwata N. Cholinesterase Inhibitors for Lewy Body Disorders: A Meta-Analysis. Int J Neuropsychopharmacol. 2015; 19(2). pii: pyv086. doi: 10.1093/ijnp/pyv086.
11. Sultzer DL et.al for CATIE-AD Study Group. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. Am J Psychiatry. 2008 Jul;165(7):844-54.
12. Tariot PN, et. al for the Galantamine USA Study Group. A 5 month, randomized, placebo controlled trial of galantamine in AD. Neurology 2000; 54(12): 2269-2276.
13. Brodaty H, et al Galantamine prolonged relase formulation in the treatment of mild to moderate Alzheimer's disease. Dement Geriatr Cogn Disord 2005; 20: 120-132.
14. Winblad B, et al A six-month double blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease- rivastigmine patch versus capsule. Int J Geriatr Psychiatry 2007; 22: 456-467.
15. Rogers SL, et al A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology. 1998 Jan;50(1):136-45.
16. Burns A, et al The effects of donepezil in Alzheimer's disease - results from a multinational trial. Dement Geriatr Cogn Disord. 1999 May-Jun;10(3):237-44.
17. Maher-Edwards G, et al SB-742457 and donepezil in Alzheimer disease: a randomized, placebo-controlled study. Int J Geriatr Psychiatry. 2011 May;26(5):536-44. doi: 10.1002/gps.2562. epub 2010 Sep 24.
18. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ. 2000 Dec 9;321(7274):1445-9.
19. Feldman HH, Lane R; Study 304 Group. Rivastigmine: a placebo controlled trial of twice daily and three times daily regimens in patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2007 Oct;78(10):1056-63.
20. Rösler M, et al Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ. 1999 Mar 6;318(7184):633-8.

RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

This guide was updated by Dr Andrew Stafford, Dr Peter Tenni and Dr David Dunbabin, from a document developed in consultation with the Deprescribing Reference Group.

MAY 2019

21. Isik, A, et al Cardiovascular outcomes of cholinesterase inhibitors in individuals with dementia: a meta-analysis and systematic review. J Am Geriatr Soc.2018 doi:10.1111/jgs.15415
22. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593.
23. Lopez OL, et al Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. J Neurol Neurosurg Psychiatry 2009; 80(6): 600-607.
24. Howard R, et al et al Nursing home placement in the donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO-AD) trial: secondary and post-hoc analyses. Lancet Neurol 2015; 14: 1171-81.
25. Guideline Adaptation Committee. Clinical Practice Guidelines and Principles of Care for People with Dementia. Sydney. Guideline Adaptation Committee; 2016. Available at http://sydney.edu.au/medicine/cdpc/resources/dementia-guidelines.php
26. http://www.pbs.gov.au/medicine/item/2479L accessed 1st August 2018
27. O'Brien JT, et al Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. Journal of psychopharmacology. 2017;31(2):147-68.
28. Dementia: assessment, management and support for people living with dementia and their carers [NG97]. 2018; London, United Kingdom: National Institute for Health and Care Excellence. Available at https://www.nice.org.uk/guidance/ng97 accessed 1st August 2018
29. Adverse Drug Reactions Advisory Committee. Cholinesterase inhibitors and cardiac arrhythmias. Aust Adv Drug React Bull 2004 (23(5): 3
30. Medicines Safety Update No 5. Cholinesterase inhibitors and syncope. Aust prescriber 2010; 33(5): 156.
31. Ali TB, Schleret TR, Reilly BM, Chen WY, Abagyan R. Adverse effects of cholinesterase inhibitors in dementia, according to the pharmacovigilance databases of the United-States and Canada. PLoS ONE 2015; 10(12): e0144337. Doi: 10.1371/journal.pone.0144337.
32. Shi X, Lin X, Hu R, Sun N, Hao J, Can G. Toxicological differences between NMDA receptor antagonists and cholinesterase inhibitors. Am J Alz Dis and Oth Dem 2016. DOI: 101177/1533317515622283.
33. Kroger E, Mouls M, Wilchesky M et al Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from Vigibase. Ann Pharmacother 2015; 49(11): 1197-1206.
34. Venalainen O, et al Adverse drug reactions associated with cholinesterase inhibitors-sequence symmetry analyses using prescription claims data. Journal of the American Medical Directors Association. 2017;18(2):186-9.
35. Reeve E, et.al. Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine. Sydney: The University of Sydney; 2018.
36. Renn BN, et al A systematic review of practice guidelines and recommendations for discontinuation of cholinesterase inhibitors in dementia. Am J Geri Psych. 2018;26(2):134-47.
37. Herrmann N, Black SE, Li A, Lanctot KL. Discontinuing cholinesterase inhibitors: results of a survey of Canadian dementia experts. International Psychogeriatrics 2011; 23(4): 539-545.
38. Dementia: assessment, management and support for people living with dementia and their carers [NG97]. 2018; London, United Kingdom: National Institute for Health and Care Excellence. Available at https://www.nice.org.uk/guidance/ng97 accessed 1st August 2018
39. Bidzan L, Bidzan M. Withdrawal syndrome after donepezil cessation in a patient with dementia. Neurol Sci 2012; 33: 1459-1461.
40. Minett TSC, et al What happens when donepezil is suddenly withdrawn? An open label trial in dementia with Lewy bodies and Parkinson's disease with dementia. Int J Geriatr Psychiatry 2003; 18: 988-993.
41. Scarpini E,. et al Cessation vesus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. J Alz Dis 2011; 26: 211-220.
42. Howard R,. et al Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012; 366:893-903.
43. Herrmann N,. et al A randomised placebo-controlled discontinuation study of cholinesterase inhibitors in institutionalised patients with moderate to severe Alzheimer's disease. J Postacute and Long term Care Med (JAMDA) 2015: doi; 10.1016/j.jamda.2015.08.019
44. O'Regan J, Lanctot KL, Mazereeuw G, Herrmann N. Cholinesterase inhibitor discontinuation in patients with Alzheimer's disease: A meta-analysis of randomised controlled trials. J Clin Psychiatr 2015; 76(11): e1424-e1431.

CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES
www.consultantpharmacyservices.com.au

phn TASMANIA
An Australian Government Initiative
primary health TASMANIA
www.primaryhealthtas.com.au