A GUIDE TO

deprescribing

phn TASMANIA
An Australian Government Initiative

primary health TASMANIA

CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

CHOLINESTERASE INHIBITORS

KEY POINTS

For the majority of people, the efficacy of cholinesterase inhibitors is modest, and it is unclear whether improvements shown in trials using various objective scoring systems translate into changes that impact clinically in terms of a person's daily care and supervision requirements.

It is unclear whether cessation of a cholinesterase inhibitor results in a clinically significant decline in cognition or other dementia symptoms.

Decisions about whether to discontinue cholinesterase inhibitors should be individualised and not arbitrarily based on single factors such as duration of treatment or MMSE score.

People who have major changes in their life circumstances (such as significant deterioration of health) should have their cholinesterase inhibitor use reviewed for ongoing clinically meaningful benefit.

People who have side effects consistent with cholinesterase inhibitor use should have a trial of cessation of the agent. People with severe side effects should have the agents ceased.

CONTEXT

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

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 independent	**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

RECOMMENDED DEPRESCRIBING STRATEGY

Australian guidelines recommend that if discontinuation is to be considered, this should be undertaken as an initial trial with close monitoring for discontinuation syndromes or a worsening in the symptoms of dementia.

A trial of deprescribing may be considered in a person with Alzheimer's disease, dementia with Lewy bodies (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 strength of formulation is reached, then maintaining this dose for a further four weeks before cessation. If there is a need for more urgent cessation of 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 and for some time after cessation. The cholinesterase inhibitor may be restarted if there is evidence that the person's condition has deteriorated and this cannot be explained by any factor other than cessation of the cholinesterase inhibitor.

BACKGROUND

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are predominantly prescribed to improve cognitive function in people with Alzheimer's disease but are also frequently used in other forms of dementia including vascular dementia and DLB.[1]

Approximately 30% of Australians over the age of 85 have dementia and over 50% of residents in permanent residential care are diagnosed with dementia.[1]

Over the next 40 years the total number of people in Australia with dementia is expected to approximately triple.

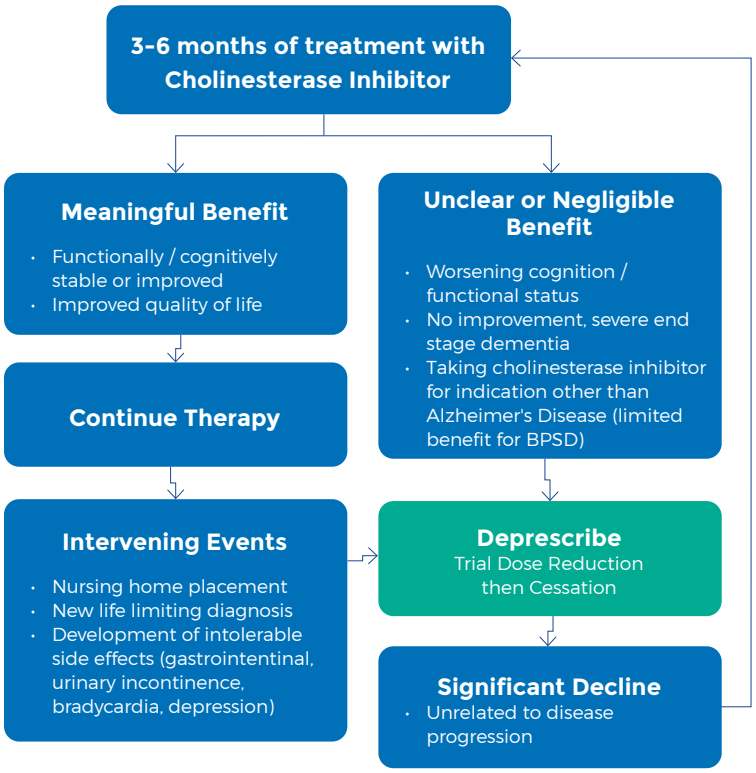

Figure 1: Deprescribing Algorithm for Cholinesterase Inhibitors

EFFICACY

By inhibiting the synaptic metabolism of acetylcholine, cholinesterase inhibitors enhance cortical cholinergic neurotransmission, with the intention of improving or stabilising cognition and delaying the onset or progression of some dementia symptoms.[2]

The efficacy of the cholinesterase inhibitors was reviewed and analysed by Tan et al in 2014.[3] They utilised a broad 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

Alzheimers disease

Tan et al. reviewed 12 studies of cholinesterase inhibitors (donepezil 6 studies, galantamine 3 studies, rivastigmine 3 studies). All studies evaluated people with mild to moderate dementia in people with a mean age of 74 years, and ~ 2/3 of the participants were female. All the trials analysed by Tan et al used the Alzheimer's disease Assessment Scale-Cognitive Subscale (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). All three cholinesterase inhibitors showed similar small 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), few studies of cholinesterase inhibitors are available (donepezil 4 studies[4,5,6,7] galantamine 1 study[8]). All of these studies involved people with advanced disease (MMSE 6-9) and used the Severe Impairment Battery (SIB) to evaluate cognitive benefit. The SIB scale scores for participating people were in the 50-70 range (out of a maximum score 100) and improvements of ~5 points on this scale were shown over 6 months. There were widely variable benefits with large standard deviations around the differences. In addition, the slight improvement in cognitive function often failed to translate into improvement in overall activities of daily living.[8,4,5,6]

Other Dementias

Types of dementia other than Alzheimer's disease respond variably to cholinesterase inhibitors. Whilst no benefit has been demonstrated in frontotemporal dementia, there appears to be a role for cholinesterase inhibitors in people with Parkinson's disease dementia or DLB. In the mild to moderate stages of DLB, cholinesterase inhibitors are usually effective, improving global cognitive function, and reducing visual hallucinations and other behavioural symptoms.[9]

In a systematic review of cholinesterase inhibitors for Parkinson's disease,[10] there was a slowing of cognitive decline in four studies. This was determined by a mean difference in MMSE of 1.12 points (95% CI 0.61 to 1.64) over a period of 10-24 weeks from a starting MMSE of 19-27.[10] A large trial by Mori et al. examined oral donepezil in DLB patients (n=140) with a randomized, placebo-controlled study design. They found mean improvement on the MMSE to be 3.8 points (95% CI 2.3–5.3; p<0.001) after donepezil was given for 12 weeks at 5 mg/day. Besides noting significant cognitive benefit, there were also significant changes in behavioural symptoms and caregiver burden.[11]

BEHAVIOURAL SYMPTOMS

A 2020 comparative effectiveness review by Fink et al. identified one eligible study (n=272) comparing the efficacy of donepezil versus placebo for treating agitation in dementia.[12] Participants initially were randomised to donepezil up to 10 mg daily, risperidone, or placebo for 12 weeks. For efficacy, low strength evidence showed no difference between treatments for change in agitation, but no studies reported data on aggression, psychosis, or disinhibited sexual behaviour at 2 weeks or longer, or on depression, anxiety, or quality of life at 24 weeks or longer. A systematic review by Sibert et al. also proposed there is insufficient evidence for the use of cholinesterase inhibitors to treat behavioural and psychological symptoms of dementia (BPSD) in Alzheimer's dementia.[13] Tariot et al. measured BPSD as a primary outcome by using the Neuropsychiatric Inventory – Nursing Home Version (NPI-NH), which showed a nonsignificant difference between donepezil and placebo (MD 2.60; 95% CI: [– 2.67, 7.78]). There was no significant improvement in either group in the NPI-NH score. The quality of evidence of this outcome according to GRADE was low.[14]

These results highlight the lack of evidence regarding the benefit of cholinesterase inhibitors on BPSD in frail older and significantly functionally impaired patients with Alzheimer's disease.

In another retrospective study looking at deprescribing of cholinesterase inhibitors in a study of nursing home residents with severe Alzheimer's dementia, it was found that **deprescribing was not associated with an increase in aggressive behaviours or incident antipsychotic prescriptions.** These findings suggest that deprescribing may be a feasible strategy to reduce medication burden in this population with no significant negative effect on behavioural symptoms or the continued use of antipsychotics.[15]

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[8,16,17] and 1 rivastigmine). Donepezil 5mg daily did not change the ADCS-ADL score; however, 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 tool scores subjects as being very much improved, much improved, minimally improved, not changed, minimally worsened, moderately worsened, or markedly worsened. Studies commonly amalgamate all positive outcomes and all negative/neutral outcomes 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 Clinicians' Global Impression of Change (CGI-I) as a measure (5 donepezil,[5,6,19,20,21] three galantamine,[16,17,22] two rivastigmine[23,24]). Each of the agents had a higher likelihood of improvement of CGI-I 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 between 23 and 34% of people who received a cholinesterase inhibitor, compared to between 15 and 29% in people who received 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 CIBIC-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.[5,17,21,22]

OTHER EFFECTS

There is some evidence suggesting an association between cholinesterase inhibitor use in dementia and 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.[25]

SUMMARY OF EFFICACY

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 translate into meaningful improvements indaily care and supervision requirements.

Amidst this summary data there appear to be patient groups who derive greater benefit from cholinesterase inhibitor therapy and those who do not . 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.

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

GUIDELINES FOR CHOLINESTERASE INHIBITOR USE

Australian clinical practice guidelines for dementia in Australia support the use of cholinesterase inhibitors for symptomatic treatment of Alzheimer's disease.[27] 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. 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).[28]

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.[30] In contrast to the Australian guidelines, neither the British Association for Psychopharmacology nor the 2018 NICE Guidelines recommend cholinesterase inhibitors be used for vascular dementia, unless it is suspected that Alzheimer's disease, Parkinson's disease dementia or DLB is also present.[31]

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. (see **Table 1**)

A study by Niznik, Joshua D et al. found that deprescribing of cholinesterase inhibitors was associated with a 36% reduced likelihood of serious falls or fractures (aOR = 0.64; 95% CI = 0.56-0.73; P < .001).

Deprescribing cholinesterase inhibitors was not associated with a significant increase in the likelihood of negative events including hospitalisations and death and was associated with a reduced likelihood of falls and fractures in older NH residents with dementia. The findings suggest that deprescribing cholinesterase inhibitors is a reasonable approach to reduce the risk of serious falls or fractures without increasing the risk of hospitalisation or death.[32]

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.[33,34] Analysis of pharmacovigilance databases in the USA and Canada,[35,36] and of the Vigibase worldwide adverse drug reactions database[37] indicate cardiac disorders and gastrointestinal disorders are 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.[38] Additional epidemiological findings have emphasized that compared with non-treatment, long-term cholinesterase inhibitor treatment may be associated with greater risks of weight loss, urinary incontinence (and the addition of anticholinergic medications to treat this), bradycardia, drug-drug interactions, and depression. These adverse consequences are unpredictable; therefore it can be challenging to assess the anticipated benefits against anticipated harms of continued treatment.[39]

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

Table 1: Common adverse effects to cholinesterase inhibitors

PBS REQUIREMENTS

For PBS subsidized treatment with cholinesterase inhibitors to continue; prescribers must ensure patients meet certain clinical criteria. The criteria includes that the patient must demonstrate a clinically meaningful response to the initial treatment.[29] This must include a comprehensive assessment which must be documented and involve the patient, carer or patient's family and the treating physician to establish agreement that treatment is continuing to produce worthwhile benefit.[29] The criteria stipulate that treatment should cease if there is no agreement of benefit as there is always the risk of harm from unnecessary use. Re-assessment for a clinically meaningful response is to be undertaken and documented every six months.[29]

Clinical meaningful response to treatment is demonstrated by:

- Improvement in the patient's quality of life including but not limited to level of independence and happiness
- Patient's cognitive function including but not limited to memory, recognition and interest in their environment
- Patient's behavioural symptoms, including but not limited to hallucination, delusions, anxiety, marked agitation or associated aggressive behaviours[29]

DISCONTINUATION SYNDROMES

There are case reports of people experiencing withdrawal symptoms after stopping cholinesterase inhibitors.[44,45] The symptoms reported include 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.

A Cochrane review published in 2021 reviewed studies of discontinuation vs continuation of cholinesterase inhibitors in patients with Alzheimer's disease (severities ranging from mild to very severe).[46] A number of outcomes were considered. Cognitive decline was evident in the short term (2 months or less), but intermediate and long-term changes in cognition were no different between continuation or discontinuation.[46] Other outcomes assessed included functional impairment, quality of life, mortality and rate of nursing home institutionalisation. No difference in these outcomes was shown in patients who discontinued or continued cholinesterase inhibitors.[46]

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.

FACTORS TO CONSIDER

Several publications that provide guidance on deprescribing cholinesterase inhibitors have been released,[39,40] 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 inhibitor 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.[41] It is inappropriate to arbitrarily cease cholinesterase inhibitors in people with Alzheimer's disease due to disease severity alone.[42]

IN FAVOUR OF DEPRESCRIBING

At any time during treatment, the presence of adverse effects (e.g., severe nausea, urinary incontinence, vomiting, weight loss, anorexia) 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 as a high priority 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, in the absence of other medical conditions (e.g., presence of delirium, significant concomitant medical illness) or change in environmental factors that may have contributed significantly to the observed decline.

Deprescribing may be considered in patients where medication adherence is poor and precludes the safe ongoing use of the medication or the ability to assess the effectiveness of the medication.

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 (dependence in most basic activities of daily living, inability to respond to environment or limited life expectancy) 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.

People who clearly clinically deteriorate after cessation of a cholinesterase inhibitor may benefit from reintroduction of the agent.

Cholinesterase inhibitors should not be discontinued in patients who currently have clinically significant psychotic symptoms, agitation, or aggression until these symptoms have stabilised (unless these symptoms appear to have been worsened by the initiation of a cholinesterase inhibitor or an increase in cholinesterase inhibitor dose).[43]

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. Hershey LA, Coleman-Jackson R. Pharmacological Management of Dementia with Lewy Bodies. Drugs Aging. 2019;36(4):309-319. doi:10.1007/s40266-018-00636-7
10. Pagano G, et al. Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatr 2015; 86: 767-773.
11. Mori E, Ikeda M, Kosaka K; Donepezil-DLB Study Investigators. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. Ann Neurol. 2012 Jul;72(1):41-52. doi: 10.1002/ana.23557. PMID: 22829268; PMCID: PMC3504981.
12. Fink HA, Hemmy LS, Linskens EJ, Silverman PC, MacDonald R, McCarten JR, Talley KMC, Desai PJ, Forte ML, Miller MA, Brasure M, Nelson VA, Taylor BC, Ng W, Ouellette JM, Greer NL, Sheets KM, Wilt TJ, Butler M. Diagnosis and Treatment of Clinical Alzheimer's-Type Dementia: A Systematic Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 Apr. Report No.: 20-EHC003. PMID: 32369312.
13. Seibert M, Mühlbauer V, Holbrook J, Voigt-Radloff S, Brefka S, Dallmeier D, Denkinger M, Schönfeldt-Lecuona C, Klöppel S, von Arnim CAF. Efficacy and safety of pharmacotherapy for Alzheimer's disease and for behavioural and psychological symptoms of dementia in older patients with moderate and severe functional impairments: a systematic review of controlled trials. Alzheimers Res Ther. 2021 Jul 16;13(1):131. doi: 10.1186/s13195-021-00867-8. PMID: 34271969; PMCID: PMC8285815.
14. 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.
15. Niznik JD, Zhao X, He M, Aspinall SL, Hanlon JT, Nace D, Thorpe JM, Thorpe CT. Impact of deprescribing AChEIs on aggressive behaviors and antipsychotic prescribing. Alzheimers Dement. 2020 Apr;16(4):630-640. doi: 10.1002/alz.12054. Epub 2020 Feb 13. PMID: 32052930; PMCID: PMC7138718.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.

22. 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.
23. 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.
24. 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.
25. 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
26. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593.
27. 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
28. http://www.pbs.gov.au/medicine/item/2479L accessed 31/5/2022
29. https://www.pbs.gov.au/pbs/search?, accessed 22/03/2022
30. 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.
31. 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
32. Niznik JD, Zhao X, He M, et al. Risk for Health Events After Deprescribing Acetylcholinesterase Inhibitors in Nursing Home Residents With Severe Dementia. J Am Geriatr Soc. 2020;68(4):699-707. doi:10.1111/jgs.16241
33. Adverse Drug Reactions Advisory Committee. Cholinesterase inhibitors and cardiac arrhythmias. Aust Adv Drug React Bull 2004 (23(5): 3
34. Medicines Safety Update No 5. Cholinesterase inhibitors and syncope. Aust prescriber 2010; 33(5): 156.
35. 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.
36. 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.
37. 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.
38. 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.
39. Renn BN, Asghar-Ali AA, Thielke S, Catic A, Martini SR, Mitchell BG, Kunik ME. A Systematic Review of Practice Guidelines and Recommendations for Discontinuation of Cholinesterase Inhibitors in Dementia. Am J Geriatr Psychiatry. 2018 Feb;26(2):134-147. doi: 10.1016/j.jagp.2017.09.027. Epub 2017 Oct 10. PMID: 29167065; PMCID: PMC5817050.
40. Reeve E, et.al. Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine. Sydney: The University of Sydney; 2018.
41. 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.
42. 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/chapter/Recommendations#pharmacological-interventions-for-dementia accessed 31/5/2022
43. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R Jr, Montero-Odasso M, Rockwood K, Rosa-Neto P, Seitz D, Sivananthan S, Smith EE, Soucy JP, Vedel I, Gauthier S; CCCDTD5 participants. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimers Dement. 2020 Aug;16(8):1182-1195. doi: 10.1002/alz.12105. Epub 2020 Jul 29. PMID: 32725777; PMCID: PMC7984031.
44. Bidzan L, Bidzan M. Withdrawal syndrome after donepezil cessation in a patient with dementia. Neurol Sci 2012; 33: 1459-1461.
45. 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.
46. Parsons C, Lim WY, Loy C, McGuinness B, Passmore P, Ward SA, Hughes C, Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia, Cochrane Database of Systematic Reviews 2021, John Wiley & Sons, Ltd. 1465-1858 DOI: 10.1002/14651858.CD009081.pub2 https://doi.org//10.1002/14651858.CD009081.pub2

AUTHORSHIP

This guide was prepared for Primary Health Tasmania by Bridget Williams and reviewed by the Deprescribing Project Advisory Group, Angus Thompson, Pharmacist Clinical Editor, Primary Health Tasmania and Dr David Dunbabin, Geriatrician.

DEPRESCRIBING PROJECT ADVISORY GROUP

DECEMBER 2022