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CHOLINESTERASE INHIBITORS

🔖 KEY POINTS

- **Efficacy of cholinesterase inhibitors is modest.**

- **It is unclear whether improvements shown in trials using objective scoring systems would translate into changes for a patient'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.**

- **Individualised decisions about discontinuing cholinesterase inhibitors should be made rather than being based on single factors such as MMSE score.**

- **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**

📎 CONTEXT

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

📎 RECOMMENDED DEPRESCRIBING STRATEGY

See page 2 for Deprescribing Algorithm.

📎 BACKGROUND

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are prescribed to improve cognitive function in patients with Alzheimer's disease, a condition that is expected to triple in prevalence by 2050.[1] Approximately 30% of Australians over 85 had a diagnosis of dementia in 2015 and in the same year, over 50% of patients in permanent residential care had a diagnosis of dementia.[1]
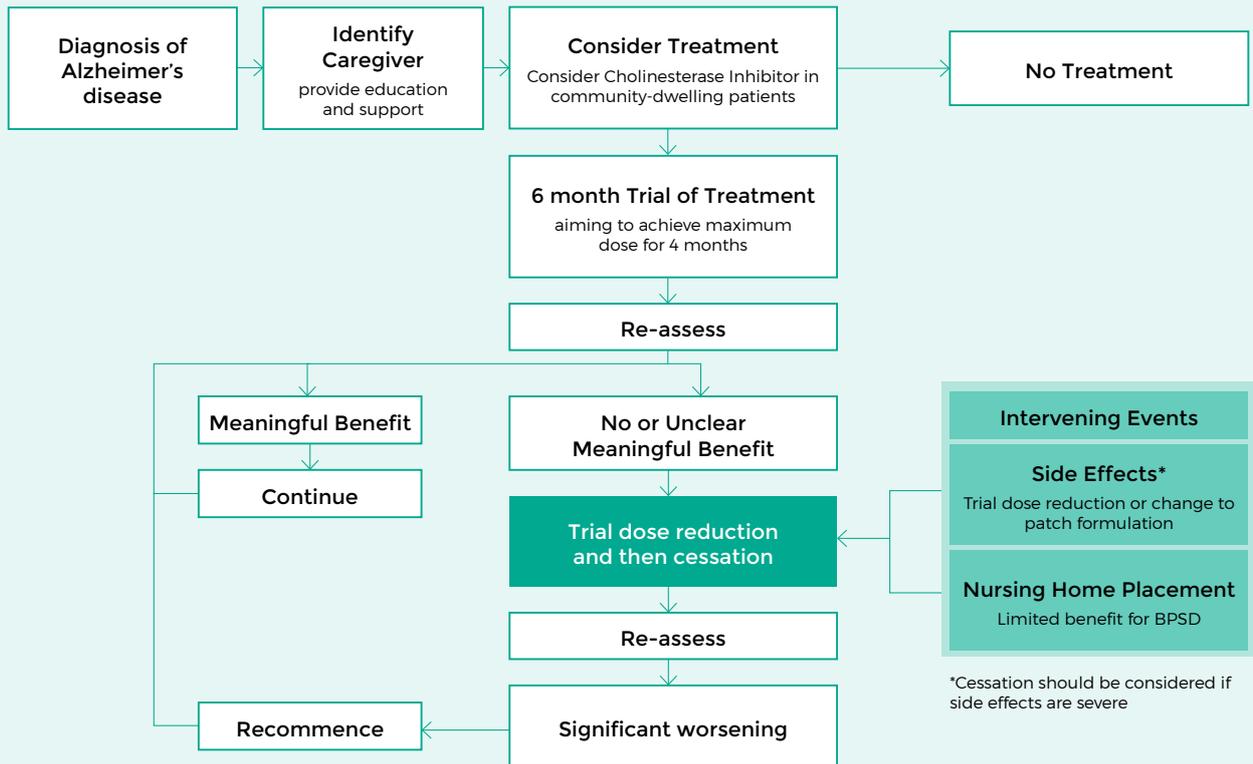
📎 EFFICACY

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.

DEPRESCRIBING ALGORITHM

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┌──────────────┐   ┌──────────────┐   ┌─────────────────────────┐      ┌──────────────┐
│ Diagnosis of │ → │  Identify    │ → │   Consider Treatment    │  →   │ No Treatment │
│ Alzheimer's  │   │  Caregiver   │   │ Consider Cholinesterase │      │              │
│   disease    │   │ provide      │   │ Inhibitor in            │      │              │
│              │   │ education    │   │ community-dwelling      │      │              │
│              │   │ and support  │   │ patients                │      │              │
└──────────────┘   └──────────────┘   └─────────────────────────┘      └──────────────┘
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6 month Trial of Treatment
aiming to achieve maximum dose for 4 months

Re-assess

Meaningful Benefit

Continue

No or Unclear Meaningful Benefit

Trial dose reduction and then cessation

Re-assess

Recommence

Significant worsening

Intervening Events

Side Effects*
Trial dose reduction or change to patch formulation

Nursing Home Placement
Limited benefit for BPSD

*Cessation should be considered if side effects are severe

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 patients with more severe Alzheimer's disease (MMSE <10), four studies of cholinesterase inhibitors are available (donepezil 3 studies[4,5,6] galantamine 1 study[7]). 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. [4,5,6,7]

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,[8] 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.[8] The impact of cholinesterase inhibitors for Lewy Body Disorders was reviewed by Matsunaga et al in 2015. 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.[9]

⊘ EFFICACY

BEHAVIOURAL SYMPTOMS

Tan et al reviewed 6 cholinesterase inhibitor studies (donepezil 3, rivastigmine 1, galantamine 2) that use the Neuropsychiatric Inventory (NPI) to score behavioural outcomes in patients 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. 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.[10]

In the Lewy Body disease meta-analysis,[9] 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.[9]

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 [7,11,12] and 1 rivastigmine[13]). 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] ten studies addressed the global benefit of cholinesterase inhibitors for Alzheimer's Dementia using the CIBIS-Plus as a measure (5 donepezil,[5,6,14,15,16] three galantamine,[11,12,17] two rivastigmine[18,19]). 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]

⊘ FACTORS TO CONSIDER

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

Clinically meaningful response to treatment is demonstrated in the following areas:

- ■ 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 environment;
- ■ Patient's behavioural symptoms, including but not limited to hallucination, delusions, anxiety, marked agitation or associated aggressive behaviour.

Amongst dementia experts, 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.[31]

IN FAVOUR OF DEPRESCRIBING

- ✔ Presence of side effects that impact on quality of life and clinical symptoms should prompt a review of the ongoing need for the agent

- ✔ Patients who have had a trial of therapy (as per the PBS) and have not demonstrated a clinically meaningful response should be considered for discontinuation of the cholinesterase inhibitor.

- ✔ Patients who have a major change in life circumstances such as admission to residential care should have their use of cholinesterase inhibitors reassessed. In such cases, benefit from cognitive enhancing therapy may no longer be relevant to the main symptoms of concern.

AGAINST DEPRESCRIBING

- ✖ Patients who demonstrate ongoing, meaningful clinical benefit (functionally stable, cognitively stable) should continue on the medication with ongoing monitoring for continued benefit or the development of any adverse effects.

- ✖ Patients dwelling in the community (as opposed to in residential care) with adequate functional capacity (in terms of activities of daily living or similar) and an appropriate support mechanism may continue to derive benefit and possible will have a delay in nursing home admission.

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

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. Irreversible inhibitors of cholinesterase include organophosphate insecticides and nerve agents (including sarin).[25]

The most frequent adverse effects associated with the cholinesterase inhibitors used for dementia are related to the gastrointestinal system. Common symptoms include nausea, vomiting and diarrhoea and these symptoms seem worse 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.

A number of other, often serious adverse effects are possible. These include cardiac effects, effects on pulmonary function and adverse impact on CNS functions.

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.[26,27] Analysis of pharmacovigilance databases in the USA and Canada,[28,29] and of the Vigibase worldwide adverse drug reactions database[30] support cardiac disorders and gastrointestinal disorders as frequently reported adverse 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

DISCONTINUATION SYNDROMES

There are case reports of patients experiencing withdrawal symptoms after stopping cholinesterase inhibitors.[32,33] The symptoms reported consisted of significant anxiety and worsening of dementia 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 patients to either continue galantamine or change to a placebo after having taken galantamine for 12 months.[34] There were no differences in the number of patients who had a decline in the ADAS-Cog of 4 points or more and no difference in the global assessment (using CIBIC-Plus).[34] In the DOMINO-AD trial,[35] patients 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, patients 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).[35] A smaller study of 40 patients showed no difference in MMSE after cessation of cholinesterase inhibitors in institutionalised patients.[36] A meta-analysis review of these and two other studies concluded that the net reduction in MMSE was 0.29 points (95%CI 0.13 to 0.45).[37]

These studies largely examine the effects of discontinuing a cholinesterase inhibitor in patients that have been previous responders to therapy. As such, cessation may result in a reduction in previously achieved benefit. Decisions about whether to discontinue cholinesterase inhibitors should be individualised and not arbitrarily based on single factors such as duration of treatment or MMSE scores.[38]

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RESOURCES

AUTHORSHIP

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