Cochrane Library

Cochrane Database of Systematic Reviews

Donepezil for dementia due to Alzheimer's disease (Review)

Birks JS, Harvey RJ

Birks JS, Harvey RJ.
Donepezil for dementia due to Alzheimer's disease.
Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD001190.
DOI: 10.1002/14651858.CD001190.pub3.

www.cochranelibrary.com

WILEY

[Intervention Review]

Donepezil for dementia due to Alzheimer's disease

Jacqueline S Birks[1], Richard J Harvey[2]

[1]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK. [2]Medical School, Deakin University and Private Practice, North Geelong, Australia

Contact address: Jacqueline S Birks, Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Botnar Research Centre, Windmill Road, Oxford, OX3 7LD, UK. jacqueline.birks@csm.ox.ac.uk.

Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 6, 2018.

Citation: Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD001190. DOI: 10.1002/14651858.CD001190.pub3.

ABSTRACT

Background

Alzheimer's disease is the most common cause of dementia in older people. One approach to symptomatic treatment of Alzheimer's disease is to enhance cholinergic neurotransmission in the brain by blocking the action of the enzyme responsible for the breakdown of the neurotransmitter acetylcholine. This can be done by a group of drugs known as cholinesterase inhibitors. Donepezil is a cholinesterase inhibitor.

This review is an updated version of a review first published in 1998.

Objectives

To assess the clinical efficacy and safety of donepezil in people with mild, moderate or severe dementia due to Alzheimer's disease; to compare the efficacy and safety of different doses of donepezil; and to assess the effect of donepezil on healthcare resource use and costs.

Search methods

We searched Cochrane Dementia and Cognitive Improvement's Specialized Register, MEDLINE, Embase, PsycINFO and a number of other sources on 20 May 2017 to ensure that the search was as comprehensive and up-to-date as possible. In addition, we contacted members of the Donepezil Study Group and Eisai Inc.

Selection criteria

We included all double-blind, randomised controlled trials in which treatment with donepezil was administered to people with mild, moderate or severe dementia due to Alzheimer's disease for 12 weeks or more and its effects compared with those of placebo in a parallel group of patients, or where two different doses of donepezil were compared.

Data collection and analysis

One reviewer (JSB) extracted data on cognitive function, activities of daily living, behavioural symptoms, global clinical state, quality of life, adverse events, deaths and healthcare resource costs. Where appropriate and possible, we estimated pooled treatment effects. We used GRADE methods to assess the quality of the evidence for each outcome.

Main results

Thirty studies involving 8257 participants met the inclusion criteria of the review, of which 28 studies reported results in sufficient detail for the meta-analyses. Most studies were of six months' duration or less. Only one small trial lasted 52 weeks. The studies tested mainly donepezil capsules at a dose of 5 mg/day or 10 mg/day. Two studies tested a slow-release oral formulation that delivered 23 mg/day. Participants in 21 studies had mild to moderate disease, in five studies moderate to severe, and in four severe disease. Seventeen studies were industry funded or sponsored, four studies were funded independently of industry and for nine studies there was no information on source of funding.

Our main analysis compared the safety and efficacy of donepezil 10 mg/day with placebo at 24 to 26 weeks of treatment. Thirteen studies contributed data from 3396 participants to this analysis. Eleven of these studies were multicentre studies. Seven studies recruited patients with mild to moderate Alzheimer's disease, two with moderate to severe, and four with severe Alzheimer's disease, with a mean age of about 75 years. Almost all evidence was of moderate quality, downgraded due to study limitations.

After 26 weeks of treatment, donepezil compared with placebo was associated with better outcomes for cognitive function measured with the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog, range 0 to 70) (mean difference (MD) -2.67, 95% confidence interval (CI) -3.31 to -2.02, 1130 participants, 5 studies), the Mini-Mental State Examination (MMSE) score (MD 1.05, 95% CI 0.73 to 1.37, 1757 participants, 7 studies) and the Severe Impairment Battery (SIB, range 0 to 100) (MD 5.92, 95% CI 4.53 to 7.31, 1348 participants, 5 studies). Donepezil was also associated with better function measured with the Alzheimer's Disease Cooperative Study activities of daily living score for severe Alzheimer's disease (ADCS-ADL-sev) (MD 1.03, 95% CI 0.21 to 1.85, 733 participants, 3 studies). A higher proportion of participants treated with donepezil experienced improvement on the clinician-rated global impression of change scale (odds ratio (OR) 1.92, 95% CI 1.54 to 2.39, 1674 participants, 6 studies). There was no difference between donepezil and placebo for behavioural symptoms measured by the Neuropsychiatric Inventory (NPI) (MD -1.62, 95% CI -3.43 to 0.19, 1035 participants, 4 studies) or by the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) scale (MD 0.4, 95% CI -1.28 to 2.08, 194 participants, 1 study). There was also no difference between donepezil and placebo for Quality of Life (QoL) (MD -2.79, 95% CI -8.15 to 2.56, 815 participants, 2 studies).

Participants receiving donepezil were more likely to withdraw from the studies before the end of treatment (24% versus 20%, OR 1.25, 95% CI 1.05 to 1.50, 2846 participants, 12 studies) or to experience an adverse event during the studies (72% vs 65%, OR 1.59, 95% 1.31 to 1.95, 2500 participants, 10 studies).

There was no evidence of a difference between donepezil and placebo for patient total healthcare resource utilisation.

Three studies compared donepezil 10 mg/day to donepezil 5 mg/day over 26 weeks. The 5 mg dose was associated with slightly worse cognitive function on the ADAS-Cog, but not on the MMSE or SIB, with slightly better QoL and with fewer adverse events and withdrawals from treatment. Two studies compared donepezil 10 mg/day to donepezil 23 mg/day. There were no differences on efficacy outcomes, but fewer participants on 10 mg/day experienced adverse events or withdrew from treatment.

Authors' conclusions

There is moderate-quality evidence that people with mild, moderate or severe dementia due to Alzheimer's disease treated for periods of 12 or 24 weeks with donepezil experience small benefits in cognitive function, activities of daily living and clinician-rated global clinical state. There is some evidence that use of donepezil is neither more nor less expensive compared with placebo when assessing total healthcare resource costs. Benefits on 23 mg/day were no greater than on 10 mg/day, and benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose, but the rates of withdrawal and of adverse events before end of treatment were higher the higher the dose.

PLAIN LANGUAGE SUMMARY

Donepezil for people with dementia due to Alzheimer's disease

Review question

What effects (benefits or harms) does donepezil have on people with dementia due to Alzheimer's disease?

Background

Alzheimer's disease is the most common cause of dementia. As the disease progresses, people lose the ability to remember, communicate, think clearly and perform the activities of daily living. Their behaviour may also change. In severe Alzheimer's disease people lose the ability to care for themselves.

The most commonly used treatment for Alzheimer's disease are medicines known as acetylcholinesterase inhibitors. Donepezil is one of these medicines. It is taken as a pill once a day.

In Alzheimer's disease, one of the changes in the brain is a reduced number of nerve cells called cholinergic neurones. These are nerve cells that signal to other cells using a chemical called acetylcholine. Acetylcholinesterase inhibitors, such as donepezil, work by preventing acetylcholine from being broken down. This may improve the symptoms of dementia. However, acetylcholine is also found elsewhere in the body and so drugs of this type may have unwanted effects.

Review methods

In this review we examined evidence about benefits and harms from studies that compared donepezil, taken for at least 12 weeks, to placebo (a dummy pill), or that compared different doses of donepezil. The studies had to be double-blind and randomised, that is, the decision whether people taking part got donepezil or placebo had to be made randomly and neither they nor the researchers should have known which treatment they were getting while the trial was going on. This was to make the comparison as unbiased, or fair, as possible. We searched for studies up to May 2017. We assessed the quality of all the studies we included. When it was sensible to do so, we analysed the results of studies together to get an overall result.

Key results

We included 30 studies with 8257 participants. Most of the people in the studies had mild or moderate dementia due to Alzheimer's disease, but in nine studies they had moderate or severe dementia. Almost all of the studies lasted six months or less. The majority of the studies were known to have been funded by the manufacturer of donepezil.

We found that people with Alzheimer's disease who took 10 mg of donepezil a day for six months did slightly better than people taking placebo, on scales measuring their cognitive function (e.g. thinking and remembering), how well they could manage their daily activities, and the overall impression of a trained researcher. We did not find any effect on behaviour or quality of life.

People taking donepezil were more likely than those taking placebo to report side effects and to drop out of the studies. Most side effects were described as mild. Nausea, vomiting and diarrhoea were most common.

Comparing 5 mg of donepezil a day with 10 mg/day, people on 5 mg had fewer side effects, but did slightly less well on cognitive function tests. A higher dose (23 mg/day) offered no advantages and was associated with more side effects.

There is some evidence that use of donepezil is neither more nor less expensive than placebo when total health care costs are taken into account.

Quality of the evidence

In general, we thought that the quality of the evidence was moderate. The main factor reducing our confidence was concern that the results of some studies might have been biased by the way they were done. We cannot be sure that the results apply to treatment longer than six months.

Conclusions

After six months of treatment, there are benefits of donepezil that are large enough to measure in studies. It is associated with side effects that are mainly mild, but that may cause people to stop treatment.

Being able to stabilise cognitive performance or ability to maintain activities of daily living may be important clinically. In terms of total healthcare costs the use of donepezil appears cost neutral. However, there does not appear to be an effect on quality of life. More data are still required from longer-term clinical studies examining measures of disease progression or time to needing full time care.