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Use of Donepezil in Alzheimer's Disease: Suggested Practice Guidelines

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Abstract

Alzheimer's disease (AD) is the cause of 60-80% of dementia (2014 Alzheimer's disease, 2014). AD is estimated to affect over 5 million people over age 65 in the US (2014 Alzheimer's disease, 2014). With the onset of baby boomers reaching the age of 65 and increased longevity it is estimated that 16 million persons will have Alzheimer's by 2050. Eighty two percent of persons with AD are over age 85. In 2014 AD is the 6th leading cause of death and the highest cost disease in the US. (2014 Alzheimer's disease, 2014)

The predicted increase in prevalence and incidence of Alzheimer's disease and longevity of the disease represents an increased disease burden on families and society and a need for effective management over many years. The purpose of this study will be to determine the effect of donepezil, a cholinesterase inhibitor, at various stages of the disease compared to placebo and to determine the best clinical practice guidelines.

The earlier the onset of donepezil therapy, the more significant effect is seen on preserving cognitive function and delayed nursing home placement. Persons at all stages (mild to very severe retain the ability to respond to donepezil. At end stage disease, it may be efficacious to discontinue donepezil.

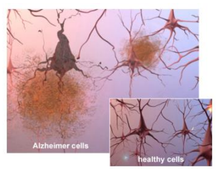
These findings indicate that health care providers need to improve the screening and early initiation of donepezil in the management of Alzheimer's disease as well as monitoring benefits and harm at later stages of the disease.

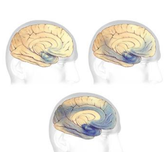
Introduction

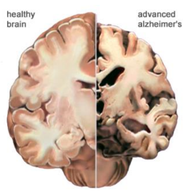
The Alzheimer's disease (AD) was discovered by Dr. Alois Alzheimer in 1907. AD is a neurodegenerative disorder resulting in damage and eventual death of neurons in the cerebral cortex resulting in dementia and eventually death. AD is described as a progressive disease that begins before clinical symptoms emerge. The first symptom of AD is memory loss that disrupts daily life often described as worsening ability to remember new information. The disease progresses to further cognitive and functional decline and in the last stage an inability to complete basic activities of daily living and decline in body function such as bathing, dressing, eating, walking, swallowing and communication is found. (2014 Alzheimer's disease, Wint & Tavee, 2014).

The hallmark of AD dementia is the accumulation of beta amyloid plaques and tau tangles resulting in synaptic dysfunction and neuron death.

Use of donepezil, a cholinesterase inhibitor (ChEI), is a first line treatment of Alzheimer's disease and is the focus of this project.







Statement of the Problem

The predicted increase in prevalence and incidence of Alzheimer's disease and longevity of the disease represents an increased disease burden on families and society and a need for effective management over many years.

Research Questions

- What is the effect of donepezil, a cholinesterase inhibitor, at various stages of the disease compared to placebo?
- What are the recommended doses of donepezil in the treatment of AD?
- What are the harms and costs of donepezil therapy?
- What is the evidence to discontinue or stop donepezil treatment?

Literature Review

Pathophysiology

Pathological findings in Alzheimer's disease include the formation of amyloid plaques, neurofibrillary tangles and loss of connection between neurons resulting in diminished cell function and death with an overall result being brain atrophy and shrinkage. (Alzheimer's disease, 2008; Winte & Tavee, 2014; Boss 2010) The loss of neurons leads to the reduction in acetylcholine a neurotransmitter at the synapse and a decrease in the amount of postsynaptic receptors of which acetylcholine acts (Bardel et al., 2011, pp 350).

Donepezil acts to bind to acetylcholinesterase which leads to an increase in acetylcholine in the synapse which enhances neurotransmission and reduces decline in cognition. Cholinesterase inhibitors do not modify the progression of AD (Bardel et al., 2011)

What is the effect of donepezil, a cholinesterase inhibitor (ChEI), at various stages of the disease compared to placebo?

Mild Cognitive Impairment (MCI):

- Bensadon and Odenheimer (2013) reported on a 2007 review that showed no effect between the ChEI and placebo groups in the probability of MCI converting to AD. A 2009 meta analysis showed a 25% risk reduction of progression of MCI to AD. Authors acknowledge flaws with the study as well as drop out rates of 21-25% in study group due to cholinergic side effects of donepezil.

Mild or early AD: Mini Mental State Exam (MMSE) 21-26

- Rountree et al. (2013) report significant improvement in cognition, maintained patient function and reduced risk of cognitive decline compared to placebo. Open label extensions demonstrated effects up to 4.9 years. Lopez (N 1539) demonstrated delay in nursing home placement with donepezil therapy.
- Mayeux (2010) concluded the effect of ChEI's to help stabilize cognition for a year and then patients may decline but slower than those on placebo thus providing clinically marginal benefits with respect to cognition, daily function and behavior.
- Birks & Harvey's (2006) Cochrane review (N5,272) concluded significant improvement in cognition at all stages of AD on 5 mg (P<0.0001) and 10 mg at 24 weeks (P<0.00001). There were more withdrawals at 10 mg due to side effects. Although statistically significant the benefit to stabilize or reduce cognitive decline is not always observed clinically.

Moderate to severe AD (MMSE score 10-20)

- Howard et al. (2012) demonstrated improvement in MMSE (p<0.001) and Basic Activity of Daily Living Score (p<0.001) with donepezil 10 mg over placebo for persons with MMSE 5-13.
- Black et al. (2007) demonstrated improvement on Severe Battery Impairment a cognitive & global function test (p<0.0001) at 24 weeks on donepezil 10 mg over placebo in persons with a MMSE 1-12.
- Molino et al. (2013) in a review of RCT 2007-2013 demonstrated improvements in cognition, global and behavioral outcomes with use of donepezil 10 mg and 23 mg.
- DiSanto et al. (2013), in a meta analysis concluded donepezil (5-10 mg) can affect cognitive, functional and behavioral outcomes at all stages of AD.

What are the recommended doses of donepezil in the treatment of AD?

- Initial dose is 5 mg which can be increased to 10 mg after 4-6 weeks.
- 23 mg/day is approved for persons with MMSE <20 who have been stable on 10 mg >3 months. (Christensen, 2012)
- Marginal differences in outcomes (N5,272) were found comparing 5 mg to 10 mg with noted increased side effects on the higher dose (Birks & Harvey, 2006).
- Wattmo et al. (N790) demonstrated 10 mg versus 5 mg of donepezil was associated with slower decline of functional ability after 3 years (Rountree et al., 2013).
- Farlow (N>1400) documented safety, tolerability & improved cognitive function 23 mg compared to 10 mg donepezil (p<0.001) for persons with MMSE 0-20. More side effects and more dropouts were noted in the 23 mg treatment group. (Christensen, 2012)

What are the harms and costs of donepezil therapy?

- Christensen (2012) reported the most common side effects of donepezil to be nausea, vomiting, diarrhea and weight loss. There are more withdrawals due to side effects with the higher dose; 5mg compared to 10, and 10 mg compared to 23 mg.
- AD was cited the most expensive disease in 2014 (Alzheimer's disease). Nursing home cost cited to be 4.5 times higher than living in the community (Khang et al., 2004)
- Brewer et al. (2012) cited (N20,729) 50% of the cohort had stopped taking their antidementia drugs within a year. Potential causes included non adherence due to cognitive decline, drug intolerance and perceived ineffectiveness of therapy.

What is the evidence to discontinue or stop donepezil treatment?

- Rountree et al. (2013) advise against temporarily stopping donepezil to watch for worsening as washouts can cause irreversible declines.
- DiSanto et al. (2013) cite improvements in cognition at all stages of AD.
- Khang et al. (2004), demonstrated donepezil use in nursing home patients with moderated to severe AD significantly maintained MMSE > placebo (p<0.05).
- Tija et al. (2014) found 36% of nursing home patients (N5,406) to still be on ChEI's with a MMSE score of 0.5-5.1.

Discussion

What is the effect of donepezil, a cholinesterase inhibitor, at various stages of the disease compared to placebo?

- In MCI there is insufficient evidence to support use of donepezil to prevent the conversion of MCI to AD. Side effects of treatment increased withdrawal rates.
- In mild to severe AD there is evidence of significant improvement in cognition with the use of donepezil over placebo. Early screening for AD and early intervention with donepezil is recommended to preserve cognitive function.

What are the recommended doses of donepezil in the treatment of AD?

- 5-10 mg is used for mild to moderate AD.
- 23 mg is approved for persons with a MMSE <20 and stable on 10 mg > 3 months.
- Significant improvements are documented in outcomes comparing 5, 10 and 23 mg to placebo. Marginal differences in outcomes was noted comparing 5 to 10 mg (Birks & Harvey, 2006). Farlow demonstrated significant improvements on 23 mg compared to 10 mg (Christensen, 2012).
- Education on medication side effects, clinical expectations and tools for drug compliance related to cognitive decline is indicated to prevent drug non-persistence and achieve maximum effective dose.

What are the harms and costs of donepezil therapy?

- Most common side effects of donepezil are nausea, vomiting, diarrhea and weight loss.
- Side effects are increased at higher doses and may result in decreased quality of life and non-persistence of medication and should be considered in determining doses.
- Side effects are worse in the first month and may be lessened by use of ER capsules and titration of 5 mg/week is suggested to achieve higher doses.
- AD was cited as the most expensive disease in 2014. Nursing home costs was reported to be 4.5 times higher in 2004 than living in the community (Khang et al., 2004)
- Lopez (N1539) demonstrated a significant delay in nursing home with donepezil monotherapy (Rountree et al., 2013).

What is the evidence to discontinue or stop donepezil treatment?

- Donepezil has been shown effective to improve cognition or stabilize cognitive decline in mild to severe stages over placebo.
- It is not recommended to stop therapy if improvements are not noted clinically as research has demonstrated its use in delayed cognitive declines.
- Evidence supports continued use of donepezil in the nursing home setting if it is in line with family values and side effects are monitored for impact on quality of life.
- Donepezil should be discontinued in very severe AD when there is palliative care.

Applicability to Clinical Practice

- AD prevalence and incidence will continue to increase with increased cost burden to families and society.
- Promote prevention of AD by staying active, eating healthy and maintaining brain stimulation.
- Recognition of MCI and treating medical causes is important as 10-15% may convert to AD.
- Awareness of the diagnosing criteria of AD, and use of MMSE to identify and measure cognition and measure changes over time is important.
- Clinical effects may be difficult to discern resulting in potential provider and patient indecision related to when to initiate titrate dose or discontinue donepezil.
- Initiation of donepezil therapy as early as possible to onset of symptoms is suggested by research to preserve cognitive function.
- Educate the patient on the anticipated side effects of donepezil, clinical expectations and memory aids to take medications as prescribed.
- Cholinergic side effects are most prominent in the first month of use.
- Initial dose is 5 mg per day and increase to 10 mg after 4-6 weeks.
- Titration of 10 mg per day dose by 5 mg per week until 23 mg/day dose is achieved is recommended for treatment of moderate to severe AD. ER formula is recommended.
- Providers should be aware that side effects of a 10 mg or 23 mg dose could be affecting quality of life and should be considered in the treatment dose.
- Research has demonstrated an ability to respond to donepezil at all stages. Cognitive preservation has been demonstrated in the nursing home setting.
- Medication decisions should be made with consideration of adverse effects and quality of life considerations.
- Donepezil should be discontinued in end stage disease where palliative care or hospice is initiated.

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