



# Dementia Drugs: When Should They Be Stopped?

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As presented at the University of Toronto's Primary Care Conference, Toronto, Ontario (May 2005)

Known as both a thief and murderer, Alzheimer's disease (AD) gradually steals the "person" from their family and then takes his/her life. The prevalence of AD doubles with every decade of life after the age of 65 and it is recognized as the fourth leading cause of death in the elderly. It is a progressive neurodegenerative disease, for which there is no cure, affecting close to 300,000 Canadians.

Dementia drugs, shown to provide modest symptomatic relief to patients with AD, were approved by Health Canada for the treatment of mild-to-moderate AD, as defined by most provincial formularies with a Folstein Mini-Mental State Examination (MMSE) score of 10 to 26. The reason for this is that randomized controlled trials (RCTs) published prior to their approval showed efficacy and safety in this patient population. Since their approval, both clinical experience and new evidence from RCTs suggest that these drugs are beneficial in the more advanced stages of AD. Also, since their approval, another Alzheimer drug, memantine, received conditional approval by Health Canada for the treatment of moderate-to-severe AD.

## Ruth's case

Ruth, 76, presents with a four-year-history of Alzheimer's disease (AD).

She was recently admitted to long-term care. At the time of her admission, Ruth's daughter Anne, reported that about three years ago her mother was started on a cholinesterase inhibitor (ChEI) by her FP. Shortly after initiating treatment, Ruth became:

- less apathetic,
- more engaged in conversations and
- started playing bridge again.

Her FP, who monitored Ruth's condition, reported that there was a slight improvement in her cognitive performance, as measured by the Folstein Mini-Mental State Examination (MMSE); however, this improvement began to wane after one year.

Despite Ruth's decline, she continued to take a ChEI until she was admitted to long-term care. At the time of her admission to the facility, Ruth's MMSE score had declined nine out of 30; yet, she was:

- still able to feed and dress herself with some assistance,
- able to maintain her social skills and
- did not exhibit disruptive behaviour.

**With a MMSE score of nine and placement in long-term care, should Ruth's treatment with a ChEI be discontinued?**

**For Ruth's followup, go to page 92.**



## When can you stop treating AD with dementia medication?

Evidence from thousands of patients enrolled in RCTs shows that groups of patients treated with cholinesterase inhibitors (ChEIs) fare better than patients treated with placebo in outcomes that measured cognition, activities of daily living and behaviour. For the clinician who treats individuals and not groups, translating this evidence into clinical practice is a challenge. AD progresses differently in each individual patient and the rate of decline, as measured by the MMSE, varies throughout the course of the

disease. After nine months to 12 months of treatment, most patients will fall back to their baseline MMSE scores and continue to decline. Does this mean that treatment is no longer effective? Probably not; symptomatic treatments ameliorate and stabilize symptoms. They are not disease-modifying and they do not prevent decline. Similar examples can be seen in the treatment of osteoarthritis with anti-inflammatory drugs or Parkinson's disease with dopaminergic agents, where the discontinuation of symptomatic treatment results in clinical deterioration. In the case of ChEIs for the treatment of AD, both clinical experience and

Table 1

### Drug trials in moderate-to-severe AD

Medication	Galantamine <i>post hoc</i> analysis <sup>1</sup>	Rivastigmine <i>post hoc</i> analysis <sup>2</sup>	Memantine monotherapy <sup>3</sup>	Memantine add-on donepezil vs. donepezil <sup>4</sup>	Donepezil <sup>5</sup>	Donepezil <sup>6</sup>
Study design	Retroactive (RCT 12 to 24 weeks)	Retroactive (RCT 26 weeks)	Prospective (RCT 12 weeks)	Prospective (RCT 28 weeks)	Prospective (RCT 24 weeks)	Prospective (RCT 24 weeks)
Population setting	Community	Community	Community	Community	Community	Nursing home
MMSE	10 to 12	16	3 to 14	5 to 14	5 to 17	1 to 10
Global function (CIBIC-plus)	√	-	NS	√	√	√
Cognition (SIB)	-	-	√	√	√	√
Cognition (ADAS-cog)	√	√	-	-	-	-
Cognition (MMSE)	√	-	NS	-	√	√
ADLs (ADCS-ADLsev)	-	-	√	√	-	√
ADLs (DAD)	NS	-	-	-	√	-

RCT: Randomized controlled trials

NS: Not significant

ADAS-cog: Alzheimer Disease Assessment Scale-Cognition

ADLs: Activities of daily living

ADLsev: Activities of daily living, severe

-: No data

CIBIC: Clinician's interview based indication of change

SIB: Severe impairment battery

ADCS: Alzheimer Disease Cooperative Study

DAD: Disability Assessment Scale for Dementia

√: Statistically significant

evidence from RCTs suggest that the discontinuation of these drugs may lead to a decline in the patient's condition, not only through a worsening of his/her cognitive function, but also to a decline in function and the emergence of behavioural symptoms (Table 1). Does this mean that one should never stop treatment? Absolutely not; however, given the lack of evidence from RCTs about the long-term use of ChEIs and the lack of clinical guidelines on when to stop treatment, the decision to stop is based purely on clinical judgment.

**Q & A** *Is there evidence to support the treatment of severe AD?*

There is mounting evidence that suggests benefits for the treatment of severe AD with ChEIs and memantine. *Post hoc* analyses of the pivotal

**Ruth's follow-up**

When Ruth entered long-term care, her physician decided to discontinue her ChEIs. Shortly thereafter, there was a precipitous decline in her ability to perform basic activities of daily living, such as dressing and feeding herself. She also appeared to be more apathetic and less engaged in social activities. As a result, her treatment with ChEIs was resumed. This resulted in some improvement in her apathy and interests; however, she did not regain her loss of activities of daily living.

trials in patients with mild-to-moderate AD, looking at subgroups of patients in the more advanced stages, showed significant benefits in patients treated with ChEIs. Donepezil has been shown to be effective in patients with moderate-to-severe AD and a recently published study showed its benefits in nursing home patients with severe AD (Figure 1). Memantine has been

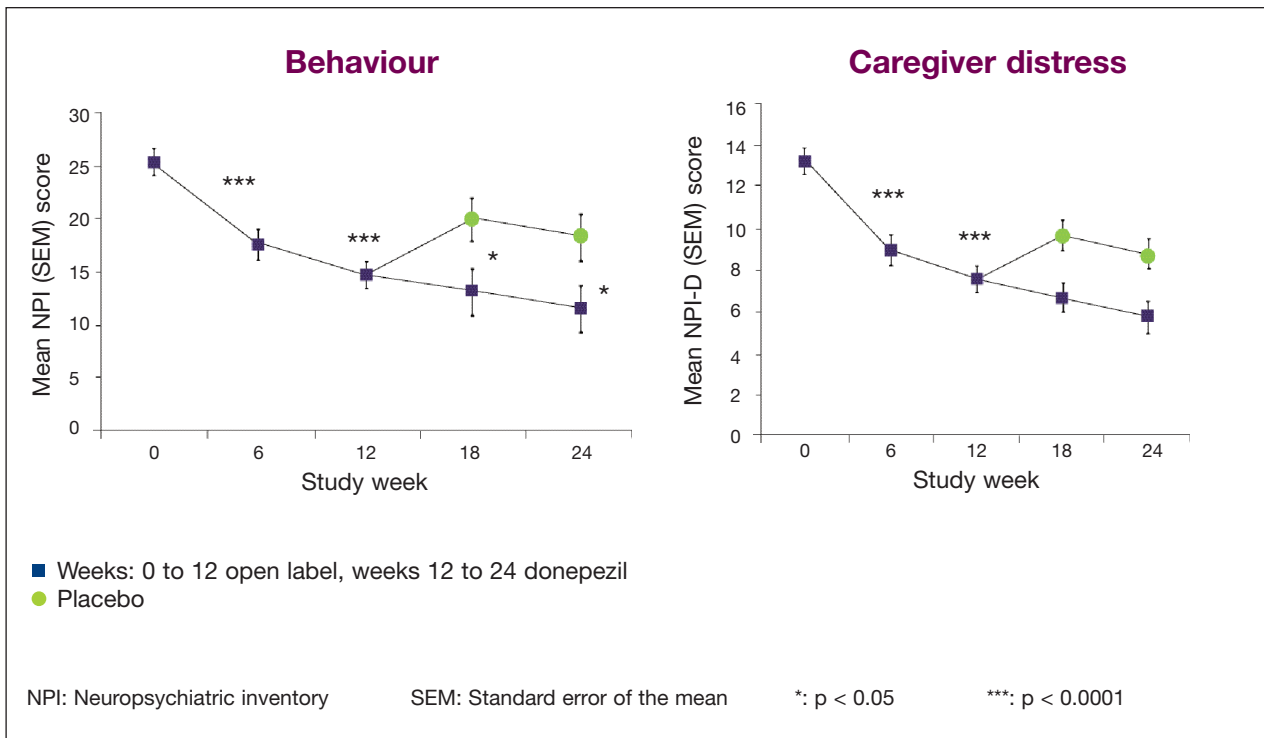


Figure 1. Donepezil randomized withdrawal study assessing the treatment of AD symptoms.<sup>7</sup>

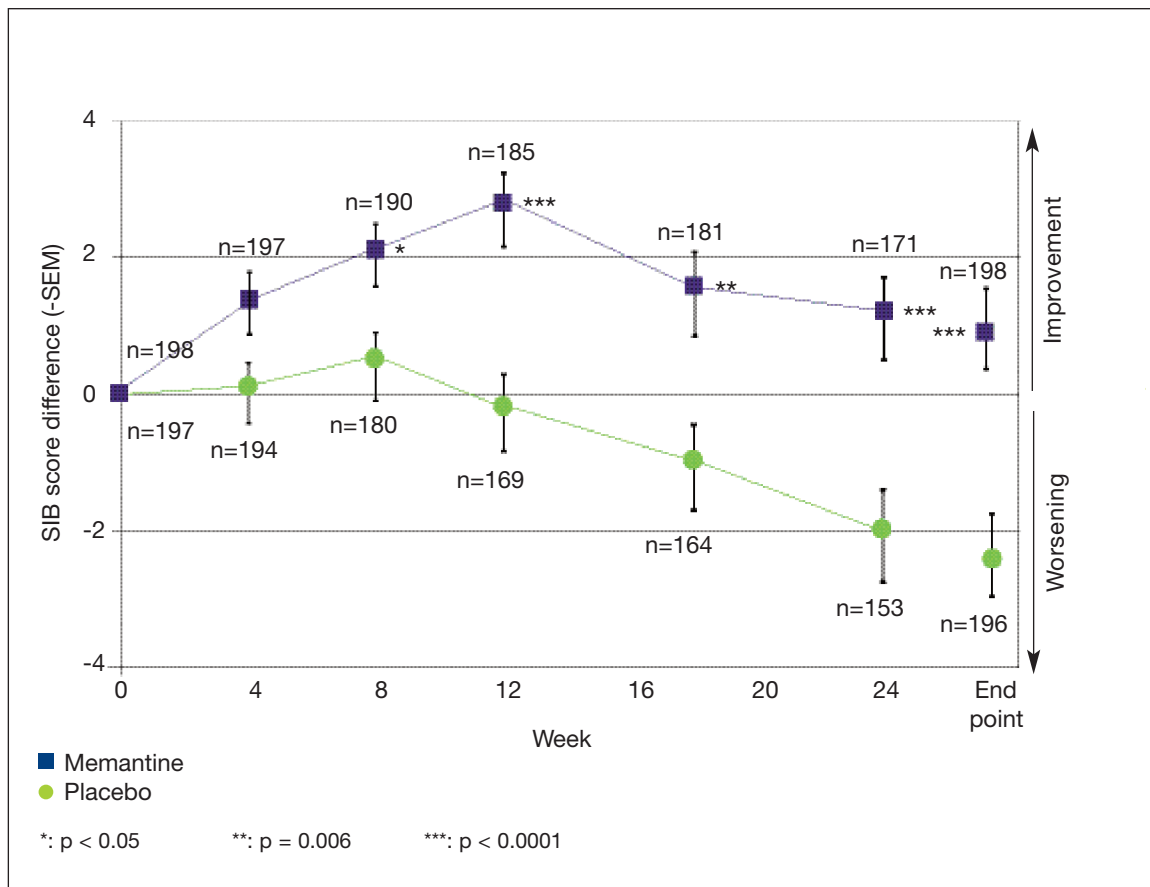


Figure 2. Cognition: SIB: mean change from baseline.<sup>4</sup>

shown to be effective as monotherapy for patients with advanced AD and as an add-on to patients who are on stable doses of donepezil (Figure 2).

**Should dementia treatment be stopped when patients enter long-term care?**


Some physicians and regulators believe that when a patient with AD enters long-term care, the severity of his/her condition warrants the discontinuation of his/her AD medication. Others would argue that placement in long-term care is not solely an indication of severity

of illness, but the cumulative result of a number of issues, including:

- the availability of able caregivers,
- financial resources and
- comorbid conditions.

The decision to stop ChEIs, or any medical treatment for that matter, should be based on:

- the risks/benefits of treatment,
- the patient’s quality of life and
- should not relate to where the patient resides.



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## Frequently asked questions

### 1. When should dementia drugs be started?

According to the Canadian Consensus Guidelines, every patient with mild-to-moderate AD should be offered a trial of ChEIs. Memantine can be used as monotherapy, or as an add-on to ChEIs in patients with moderate-to-severe AD.

### 2. When should dementia drugs be stopped?

Dementia drugs should be stopped when patients experience intolerable side-effects, or when the clinician and family perceive a lack or loss of clinical benefit. Gradual decline after one year of treatment is to be expected, even in responders.

As with all medications, clear evidence of a favorable risk/benefit ratio and quality of life should be considered when continuing treatment.

### 3. Do dementia drugs work in patients with severe AD?

There is mounting evidence that ChEIs and memantine are effective in the treatment of severe AD.

## Take-home message

- ChEIs and memantine have been shown to be effective in the treatment of severe AD
- Placement in long-term care is not an indication to stop the treatment of dementia medication or any other medication



#### References

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