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Is Rivastigmine Effective in the Treatment of Alzheimer's Disease?

Beena Patel
Philadelphia College of Osteopathic Medicine, beenapa@pcom.edu

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not rivastigmine is effective for the treatment of Alzheimer's Disease.

STUDY DESIGN: Review of two trials in the English language published in 2007 and 2010, and an open-label, singlearm, multi-center study from 2008.

DATA SOURCES: Randomized, double-blind, placebo-controlled trials comparing rivastigmine to a visually-matched capsule (placebo) was found using PubMed and Cochrane databases.

OUTCOMES MEASURED: Overall global performance using the Alzheimer's Disease Assessment Scale (ADAS-cog), ability to perform activities of daily living, cognitive function using the mini mental status exam (MMSE), and neuropsychiatric symptoms using BEHAVE-AD.

RESULTS: The two RCTs included in the review along with the open-label study showed that rivastigmine did help improve symptoms, but usually in patients with a more severe or progressive form of dementia. Rivastigmine was also shown to be more effective in preventing cognitive decline when given at higher doses and to participants who did not have other confounding symptoms, such as hallucinations.

CONCLUSIONS: The results of the RCTs and open-label study show that rivastigmine for the treatment of Alzheimer's disease is safe and effective.

KEYWORDS: Alzheimer's disease, rivastigmine, treatment

INTRODUCTION

Alzheimer's disease is a neurological condition that consists of a decline in cognition, memory and activities of daily living. Memory loss tends to involve an impaired recall of previously learned information. The two hallmark findings in brains affected by Alzheimer's are intracellular neurofibrillary tangles from the clump of hyperphosphorylated tau proteins and the extracellular senile plaques, which are made of amyloid beta protein. It has been estimated that 1 new case of AD develops every 7 seconds, with an even higher rate in developing countries.[4] More than 5 million Americans and over 10% of American citizens who are 71 years of age or older suffer from AD and the medical needs of patients affected by AD continue to be unmet. Care-givers for individuals with AD spend greater than $94 billion dollars annually on AD-related healthcare costs.[4]

While research is still searching for ways to detect Alzheimer's disease in individuals before progressive cognitive decline starts to become an issue, there is still no surefire way of preventing the inevitable from happening in people who are affected by the disease. The global cognitive status of individuals is assessed using questionnaires, such as the Mini Mental Status Exam (MMSE), Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) and Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD).[1,2] Hallucinations are a common finding in individuals affected by the disease and they are present in 20% to 40% of patients, with visual hallucinations being the most common form.[1] Current treatment includes acetylcholinesterase inhibitors, such as donepezil, galantamine and rivastigmine, in patients with mild to moderate AD.[5] Individuals with more advanced disease have shown to have some benefits from memantine alone, which is an N-methyl-D-aspartate antagonist.[5] Caregiver support and respite care are often necessary as well in order to help the individuals carry out their normal activities of daily living.

Rivastigmine has been proposed as an effective treatment for Alzheimer's disease by reducing neuropsychiatric symptoms in patients with AD who have hallucinations as well as patients who are unresponsive to other treatments[1]. In one study, it was demonstrated that switching from donepezil to rivastigmine without a washout period may still be well-tolerated and effective in patients who do not improve with donepezil.[3]

OBJECTIVE:

The objective of this systematic review is to determine whether or not rivastigmine is effective for the treatment of Alzheimer's Disease. Previous trials in this study that have studied the efficacy of rivastigmine in treating the neuropsychiatric symptoms of Alzheimer's disease have shown that it is a safe and effective alternative to other medications, such as donepezil.

METHODS:

The studies that were obtained for this analysis included individuals who were 45 years of age and older with a clinical diagnosis of Alzheimer's disease. The intervention that was used was 1 to 12 mg of rivastigmine. Comparisons to this intervention included a visually matched placebo group. The outcomes measured were overall global performance using the Alzheimer's Disease Assessment Scale (ADAS-cog), ability to perform activities of daily living, cognitive function using the mini mental status exam (MMSE), and neuropsychiatric symptoms using BEHAVE-AD. The types of studies included in this systematic review are two double-blind, placebo-controlled randomized controlled trials and an open-label, singlearm, multicenter study.

Information on these studies was gathered from databases such as Cochrane Database of Systematic Reviews, MEDLINE and PubMed. The articles were selected based upon their relevance to the question and significance of the outcomes to the patients. Inclusion criteria that were used for the selection of studies included: 1) Studies that were randomized controlled trials. 2) Studies that consisted of patient-oriented outcomes (POEMs). 3) Studies published after 1996. 4) Studies published in the English language. Exclusion criteria used to limit the selection of studies included: 1) Articles that were systematic reviews. 2) Subjects who did not fulfill the criteria for diagnosis of dementia of the Alzheimer's type. While searching for studies in the English language, specific keywords that were used included "Alzheimer's disease," "rivastigmine" and "treatment." This helped to selectively limit articles that held more significance and were more pertinent to the study. The studies that were then finalized and selected were: 1) Effects of rivastigmine in Alzheimer's disease patients with and without hallucinations, 2) Rivastigmine: a placebo controlled trial of twice daily and three times daily

regimens in patients with Alzheimer's disease, and 3) Safety and efficacy of rivastigmine in patients with Alzheimer's disease not responding adequately to donepezil: an open-label study.

The characteristics of all the studies that were used in this analysis can be found in **Table 1**.

Table 1: Demographics and Characteristics of included studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	# of withdrawal	Interventions
Feldman[2], 2007	Double-blind, placebo-controlled RCT	678	At least 50 years of age	Entry scores of 10-26 on the MMSE and met the criteria for AD	Concomitant severe/unstable cardiac disease, severe obstructive pulmonary disease or life-threatening conditions; anti-cholinergic drugs	125	Rivastigmine twice a day or three times a day with a range of dosing between 2-12 mg/day; placebo
Cummings[1] 2010	Double-blind, placebo-controlled RCT	927	Between the ages of 45 and 89 years old	Met criteria for AD, score between 10 and 26 on MMSE; concomitant controlled and manageable illnesses; with or without hallucinations	Other dementias; severe cardiac disease and obstructive pulmonary disease; malignancies; psychotropic drugs; anti-cholinergic drugs	225	6-month trials of rivastigmine capsules with flexible dosing up to 12 mg/day in 2 divided daily doses
Figiel[3], 2008	Open-label, single-arm study	270	Between ages of 50 and 90	Diagnosis of dementia of Alzheimer's type; MMSE score of 10 to 26; prior use of donepezil 10 mg/day for at least 3 months prior to baseline with poor results; concomitant major depression	advanced medical illnesses; CVA 6 months prior to baseline; uncontrolled seizure disorder; unstable asthma or obstructive pulmonary disease; medications for parkinson's disease or anticholinergics; lithium; previous exposure to rivastigmine	85	26-week treatment period with rivastigmine and flexible dosing of 3-12 mg/day

Outcomes that were measured were POEMs, such as the efficacy of medication (rivastigmine) in treating Alzheimer's disease along with the amount or dosage of medication used, changes in activities of daily living using the PDS, current cognitive function using the MMSE, ability to perform activities of daily living by the use of ADAS-cog, and the severity of neuropsychiatric symptoms using BEHAVE-AD. The Progressive Deterioration Scale (PDS) measures the changes in activities of daily living. There is a 29-item scale scored on a scale of 0 to 100, where an increase in score suggests an improvement in the patient's ability to perform activities of daily living. The Mini Mental Status Exam (MMSE) assesses memory, attention, concentration, repetition, comprehension and ability to create a sentence. It includes a 10-item assessment, with a range of 0-30 points in which a higher score represents better cognitive function. The Alzheimer's Disease Assessment Scale (ADAS-cog) has a total score range of 0-70, where a decreasing score shows improvement in cognitive function. Neuropsychiatric symptoms were obtained using the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), which is a 25-item scale that evaluates paranoid and delusional ideation (7 items), hallucinations (5 items), activity disturbances (3 items), aggressiveness (3 items), diurnal rhythm disturbances (1 item), affective disturbance (2 items), and anxieties and phobias (4 items). The items are then rated on a four-point scale (0-3) based on a clinical interview with a caregiver, with the scores assigned depending on the severity of symptoms that are observed (A score of 0 in a specific item signifies the absence of a symptom while a score of 3 represents the most severe category).

RESULTS:

The results of this review were presented as continuous data. The data in the Feldman et al and Cummings et al studies can be converted to dichotomous form. The data from all the studies were analyzed with the intention to treat, excluding those who withdrew from the study. The inclusion and exclusion criteria were fairly similar for each of the studies. The participants for all the studies consisted of individuals who were 45 years of age and older with a clinical diagnosis of Alzheimer's Disease. The studies excluded participants who did not fit the criteria for diagnosis of dementia of the Alzheimer's type and individuals who had an advanced, severe, or unstable medical condition of any type that could possibly interfere with the assessment. Patients with a cerebrovascular accident within six months of baseline, uncontrolled peptic

ulcers, severe or unstable asthma or obstructive pulmonary disease, any psychiatric diagnosis that could interfere with the response of patient to study medication, and uncontrolled active seizure disorders were excluded as well.

The study done by Figiel et al studied Rivastigmine in patients who did not respond well to prior use of donepezil. The study reported that out of 226 patients with a minimum of 1 neuropsychiatric inventory symptom at baseline, 42.0% showed greater than 30% improvement. The mean MMSE score from baseline was 18.2. The primary analysis was done at 26 weeks, where changes in efficacy from baseline were tested using paired t-tests, where a p-value < 0.05 was found to be significant. The 95% confidence interval included the percept of participants who showed improvement or no changes from baseline on the CGIC scale.[3]

In the study done by Feldman et al, Rivastigmine was given in a dose of 9.6 mg/day in the TID regimen compared to 8.9 mg/day in the BID regimen. While both regimens were shown to be beneficial to the cognitive performance in patients with Alzheimer's disease, the TID regimen demonstrated to have an even higher tolerability and was clinically effective with higher doses, further showing that the efficacy of rivastigmine may be a result of its dose. The relative benefit increase (RBI) was 63.2% and the absolute benefit increase (ABI) was 12%. The number needed to treat (NNT) was 9 patients. 9 people, thus, needed to be treated with rivastigmine in order to prevent cognitive decline in one patient with AD. The difference in the control and experimental group is statistically significant with the p-value less than 0.05.[2]

In the study done by Cummings et al, rivastigmine was clinically more effective in participants without hallucinations in comparison to those with hallucinations. The number needed to treat (NNT) was 12 patients. In those participants with hallucinations, for every one person treated, one less person would benefit from the treatment. On the other hand, 12 people need to be treated in the non-hallucinating group in order to improve the cognitive function of one individual. The relative benefit increase (RBI) in persons without hallucinations was 0.0035% and the absolute benefit increase (ABI) was 0.2%. The difference between the control and experimental groups is statistically significant with the p-value less than 0.05. **Table 2** shows a summary of the three studies and the results for the efficacy of rivastigmine in the treatment of Alzheimer's disease.[1]

Table 2. Clinical efficacy of Rivastigmine in the treatment of Alzheimer's Disease

Study	Rivastigmine group Individuals with improvement of cognitive performance	Control group Individuals with improvement of cognitive performance	p-value	RBI	ABI	NNT
Feldman et al, 2007	31%	19%	$p < 0.05$	63.2%	12%	9
Cummings et al, 2010	36%	27%	$p \leq 0.05$	0.0035%	0.2%	12
Figiel et al, 2008	42.0%	NR	$p \leq 0.05$	NR	NR	NR

RBI= Relative Benefit Increase, ABI= Absolute Benefit Increase, NNT= Number Needed to Treat,
NR= Not Reported

Each study also calculated the incidence of adverse effects regarding the safety of rivastigmine usage. In the study done by Feldman et al, the incidence of adverse events was 18% for the rivastigmine TID group, 76.2% in the BID group and 91.6% in the placebo group. The relative risk increase (RRI) was -16.9% and the absolute risk increase (ARI) was -15.5%. The number needed to harm (NNH) was 7 patients. If 7 participants are treated with rivastigmine, one less person would have a beneficial outcome, suggesting that the intervention may be harmful. Common adverse effects reported with use of rivastigmine included nausea, vomiting, anorexia and abdominal pain.[2]

The study conducted by Cummings et al showed 93% of individuals using rivastigmine compared to 78% of participants in the placebo group faced at least one adverse event. The relative risk increase (RRI) was 0.19% and the absolute risk increase (ARI) was 0.15%. The number needed to harm (NNH) was 7 patients.[1]

The Figiel et al study indicated that the incidence of adverse effects in the rivastigmine group was 82.6%. The data in this study was statistically significant with a p-value of ≤ 0.05. **Table 3** shows a summary of the incidence of adverse effects in patients in the rivastigmine group and in the control group for each study performed.[3]

Table 3 – Incidence of Adverse Events of Rivastigmine and Control Groups

Study	Rivastigmine Incidence of Adverse Events	Control Group Incidence of Adverse Events	p-value	RRI	ARI	NNH
Feldman et al, 2007	76.2%	91.6%	$p < 0.05$	-16.9%	-15.5%	-7
Cummings et al, 2010	93%	78%	$p \leq 0.05$	0.19%	0.15%	7
Figiel et al, 2008	82.6%	NR	$p \leq 0.05$	NR	NR	NR

RRI= Relative Risk Increase, ARI= Absolute Risk Increase, NNH= Number Needed to Harm, NR= Not Reported

In all three studies investigated with rivastigmine, the most common adverse effects usually pertained to gastrointestinal symptoms, such as nausea, vomiting, abdominal pain and loss of appetite. In all three studies, the incidence of adverse effects reported was higher in the rivastigmine group. Table 4 shows the incidence of gastrointestinal events that happened during the Cummings et al study on rivastigmine.[1]

Table 4. Incidence of GI adverse effects in Rivastigmine and Placebo Groups

Gastrointestinal Adverse Event	**Rivastigmine** n=356	**Placebo** n=376
Nausea	52	12
Vomiting	33	5
Abdominal Pain	12	6

n = number of participants in the group

DISCUSSION:

The Figiel et al study did not consist of a placebo or control group because there were ethical concerns of not providing treatment to participants who were already responding poorly to donepezil. However, not having a control group could have limited the findings and conclusions. Participants in a placebo group may still have deteriorated but at a slower rate. It is difficult to make conclusions about efficacy due to the lack of randomization and a control group. Results suggest that 50 to 70% of participants who did not respond to donepezil may still have shown stabilization or improvement in cognitive function with rivastigmine. Therefore, when switching a patient from donepezil to rivastigmine, the individual's behavioral performance should be taken into account as well and not just his/her cognitive and global performance. In addition, there was an overall completion rate of 69% in the study, which is debatable in terms of the true efficacy and tolerability of rivastigmine.[3] Researchers found that it is clinically possible to switch patients from donepezil to rivastigmine without a washout period (which was done in earlier trials) in order to maintain the treatment effect; this finding was taken into account later on in the study.

In the study conducted by Cummings et al, there were some discrepancies with the efficacy of rivastigmine in individuals affected by AD who had hallucinations versus those who did not have hallucinations. Further studies have shown that rivastigmine allows for a more significant benefit in patients who have a more severe or progressive form of dementia.[1] That

may play a role as to why there were larger placebo differences observed in groups with greater cognitive decline. However, this may hold some significance because other studies have shown that the cholinesterase-inhibiting activity of rivastigmine plays a central role in reducing severe neuropsychiatric symptoms; this is very helpful for researchers to be aware of because Alzheimer's disease has been linked to a reduction in the activity of cholinergic neurons.

In the Feldman et al study, rivastigmine caused a small but statistically significant decrease in the average weight in both the TID and BID groups. This led to a decrease in heart rate of individuals in both groups compared to the placebo—this may have altered the efficacy of rivastigmine. Furthermore, there were about 33% of subjects in the TID group who were receiving less than 6 mg/day during withdrawal due to adverse events and an estimated 66% were taking at least 6 mg/day while, in the BID group, about 50% were taking at least or less than 6 mg/day so the higher rate of discontinuation or withdrawal in the BID group does not necessarily reflect higher doses taken in this group and so, the reasons for discontinuation remain unknown.[2] This could have altered the significance of the findings. Additionally, although the maximally tolerated mean dose was higher for individuals in the TID group, it was noted that rivastigmine with food or shortly after a meal can improves its tolerability by reducing peak plasma concentrations of the drug and slowing its rate of increase so this could have played a role in efficacy. Also, since the drug is rapidly absorbed by the gastrointestinal tract, some patients may have not been as compliant with proper drug usage in order to avoid symptoms of nausea and vomiting.

CONCLUSIONS:

The trials that were reviewed suggest that rivastigmine is safe and effective for the treatment of Alzheimer's disease. The individuals of the studies seemed to show improvement with activities of daily living and a higher cognitive function according to the higher scores on the MMSE. Some flaws include the length of treatment, which may not have been as long of a duration to really assess whether rivastigmine is, in fact, effective in reducing the long-term cognitive decline associated with Alzheimer's disease. Studies in the future should include various medications to compare rivastigmine with and investigate the overall results and adverse effects over a more extended period of time. This, in turn, may allow future healthcare

professionals to have a better stance on what drugs may be more appropriate for their patient population and their associated symptoms. The outcomes of these future studies may help determine what may be the best pharmacological treatment of Alzheimer's disease.

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