
Brief Review: Rivastigmine, A Second Cholinesterase Inhibitor

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Since the publication of the recommendations of the Canadian Consensus Conference on Dementia, a second cholinesterase inhibitor, rivastigmine has been approved for use in Canada for the treatment of mild to moderate Alzheimer's disease.

Rivastigmine is a carbamate pseudo-irreversible acetyl cholinesterase inhibitor, which acts selectively in the brain, specifically in the hippocampus and cortex interfering with the action of acetyl cholinesterase and butyryl cholinesterase.¹

RANDOMIZED CONTROLLED TRIALS IN ALZHEIMER'S DISEASE: PIVOTAL STUDIES

Two pivotal studies have been published, each using very similar methodology. In each study, patients of either sex over a wide age range fulfilled criteria for dementia of the Alzheimer's type as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)² and had probable Alzheimer's disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).³ Participants had a baseline Mini-Mental State Examination (MMSE)⁴ score of between 10 and 26, consistent with mild to moderately severe impairment. Both pivotal studies were multicentered and supported by the product manufacturer.

The first study, published in 1998⁵ involved 699 patients at 22 sites in the USA. Participants were randomized into one of three groups: placebo, low dose rivastigmine (1-4 mg per day), and high dose rivastigmine (6-12 mg per day). An initial fixed dose phase (weeks 0-7) was followed by a flexible dose phase (weeks 8-26). For the intention-to-treat analysis, at 26 weeks the mean difference was significantly more (3.78 points (95% CI 2.69, 4.87, $p < 0.001$) in the high dose group than the placebo group on the ADAS-Cog.⁶ On the CIBC-plus scale⁷ a global measure, high dose rivastigmine resulted in a significant improvement compared to placebo ($p < 0.01$). Significant improvements were also evident on other scales. Differences in outcomes between low dose rivastigmine and placebo did not reach statistical significance.

The second pivotal study, published in 1999,⁸ was conducted at 45 centers in Europe and North America; 725 patients between the ages of 50 and 85 were randomized to receive placebo, low dose (1-4 mg) or high dose (6-12 mg) rivastigmine. In the intention-to-treat analysis at 26 weeks, outcomes were significantly better in the high dose compared to the placebo for CIBC-plus ($p < 0.001$), Progressive Deterioration Scale (PDS)⁹

($p < 0.001$) and Global Deterioration Scale (GDS)¹⁰ ($p < 0.05$) although not for the ADAS-Cog ($p < 0.1$).

SYSTEMATIC REVIEW OF RCTs

The Cochrane Database Systematic Review of Rivastigmine¹¹ combined the results of seven randomized controlled trials involving 3370 patients and concluded that at 26 weeks, high dose rivastigmine (6-12 mg per day) was associated with an improvement in cognitive function on the ADAS-Cog compared with placebo. The weighted mean difference was 2.09 points (95% CI 0.65, 1.54) in the intention-to-treat analysis. At 26 weeks, rivastigmine produced a 2.2 point improvement in activities of daily living, assessed by the PDS, weighted mean difference 2.15 points (95% CI 3.16, 1.13) in the intention-to-treat analyses. Fewer high dose patients were graded as having severe dementia at 26 weeks, 55% of patients taking rivastigmine compared with 59% taking placebo. The odds ratio was 0.78 (95% CI 0.6, 0.94).

RIVASTIGMINE IN DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies is a syndrome characterized by visual hallucinations and delusions early in the course of dementia, with fluctuations in cognitive status, spontaneous extra pyramidal signs and neuroleptic sensitivity.¹² A recently reported randomized controlled trial compared rivastigmine titrated to the highest tolerated dose to placebo in 120 subjects with probable dementia with Lewy bodies of a mild to moderate severity.¹³ Rivastigmine produced statistically significant improvement in behaviour, especially apathy, hallucinations, delusions and cognition. Almost twice as many patients on rivastigmine than placebo showed a clinically relevant improvement in the Neuropsychiatric Inventory¹⁴ in the intention-to-treat and other analyses.

PLACE IN THERAPY

There has been no direct comparison between rivastigmine and other cholinesterase inhibitors. In clinical trials, adverse effects (most commonly, nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain, and dizziness) occurred more often with rivastigmine than placebo, leading to withdrawal rates of 20-30% of patients with the higher dose (6-12 mg per day.) There have been no reports of hepatic toxicity with rivastigmine. The incidence of adverse effects may be ameliorated by slower titration of the drug.

CONCLUSION

The available evidence and the approval by Health Canada of this drug suggests that the same recommendation can be given to rivastigmine as donepezil (see page S110 of the supplement). There may also be a role for this drug in dementia with Lewy bodies.

COMMENTS

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