Doença de Alzheimer e Galantamina

Galantamine for Alzheimer's disease and mild cognitive impairment

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Synopsis

Galantamine improves global and cognitive symptoms at doses of 16 mg/day or greater, in people with mild to moderate Alzheimer's disease, for at least 6 months.

Alzheimer's disease is a progressive neurodegenerative illness, affecting thinking and memory. Galantamine is a reversible cholinesterase inhibitor that inhibits the degradation of the neurotransmitter acetylcholine, and may have other actions on nicotinic receptors as well. The review finds that galantamine was more effective than placebo in improving cognitive function. A greater proportion of people taking galantamine than of those taking placebo was rated as improved or not changed after three to six months. There was evidence of improvement on measures of activities of daily living and behavioral symptoms. Longer-term controlled studies have yet to be performed or published.

Data from the two MCI trials suggest marginal clinical benefit, but a yet unexplained excess in death rate.

Abstract

Background
Galantamine is a specific, competitive, and reversible acetylcholinesterase inhibitor.

Objective
To assess the clinical effects of galantamine in patients with mild cognitive impairment (MCI), probable or possible Alzheimer's disease (AD), and potential moderators of effect.

Search strategy
The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, last updated on 25 April 2005 using the terms galanthamin*, galantamin* and Reminyl. Published reviews were inspected for further sources. Additional information was collected from unpublished clinical research reports for galantamine obtained from Janssen and from http://www.clinicalstudyresults.org/.

Selection criteria
Trials selected were randomised, double-blind, parallel-group comparisons of galantamine with placebo for a treatment duration of greater than 4 weeks in subjects with MCI or AD.

Data collection and analysis
Data were extracted independently by the reviewers and pooled where appropriate and possible. Outcomes of interest include the clinical global impression of change (CIBIC-plus or CGIC), Alzheimer's Disease Assessment Scale-cognitive sub scale (ADAS-cog), Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL), Disability Assessment for Dementia scale (DAD) and Neuropsychiatric Inventory (NPI). Potential moderating variables of treatment effect assessed included trial duration, dose, and diagnosis of possible versus probable Alzheimer's disease.

Main results
Ten trials with a total 6805 subjects were included in the analysis.

Treatment with galantamine led to a significantly greater proportion of subjects with improved or unchanged global rating scale rating (k = 8 studies), at all dosing levels except for 8 mg/d. Confidence intervals for the ORs overlapped across the dose range of 16 mg to 36 mg per day, with point estimates of 1.6 - 1.8 when analysed with the intention-to-treat sample.

Treatment with galantamine also led to significantly greater reduction in ADAS-cog score at all dosing levels (k = 8), with greater effect over six months compared to three months. Confidence intervals again overlapped. Point estimate of effect was lower for 8 mg/d but similar for 16 mg to 36 mg per day. For example, treatment effect for 24 mg/d over six months was 3.1 point reduction in ADAS-cog (95%CI 2.6-3.7, k = 4, ITT).

ADCS-ADL, DAD and NPI were reported only in a small proportion of trials: all showed significant treatment effect in some individual trials at least. Confidence interval of treatment effect for the one trial recruiting patients with possible AD overlapped with the other seven trials recruiting patients with probable AD. Galantamine's adverse effects appeared similar to those of other cholinesterase inhibitors and to be dose related.

Prolong release / once daily formulation of galantamine at 16 - 24mg/d was found to have similar efficacy and side-effect profile as the equivalent twice-daily regime.

Data from the two MCI trials suggest marginal clinical benefit, but a yet unexplained excess in death rate.

Reviewers' conclusions
Subjects in these trials were similar to those seen in earlier anti dementia AD trials, consisting primarily of mildly to moderately impaired outpatients. Galantamine's effect on more severely impaired subjects has not yet been assessed.

Nevertheless, this review shows consistent positive effects for galantamine for trials of three to six months' duration. Although there was not a statistically significant dose-response effect, doses above 8 mg/d were, for the most part, consistently statistically significant.
significant.

Galantamine's safety profile in AD is similar to that of other cholinesterase inhibitors with respect to cholinergically mediated gastrointestinal symptoms. It appears that doses of 16 mg/d were best tolerated in the single trial where medication was titrated over a four week period, and because this dose showed statistically indistinguishable efficacy with higher doses, it is probably most preferable initially. Longer term use of galantamine has not been assessed in a controlled fashion.

Galantamine use in MCI is not recommended due to its association with an excess death rate.

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GAL-INT-6Erkinjuntti (published and unpublished data)


GAL-USA-1 Raskind (published data only)


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* indicates the major publication for the study

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