A review of the use of propentofylline in the treatment of dementia

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Authors' objectives
To assess the effectiveness of propentofylline in the treatment of dementia.

Searching
The authors searched MEDLINE, EMBASE, HealthSTAR, the Cochrane Controlled Trials Register and the NHS Centre for Reviews and Dissemination's databases (DARE NHS EED). The authors also scanned relevant health technology assessment agency resources such as web sites and booklets. Search terms used were: 'propentofylline', 'HWA285' and the CAS registry number.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and meta-analyses of phase III trials over a 12 month study period. Pilot studies and phase II studies were also included.

Specific interventions included in the review
Propentofylline for the intervention group and placebo for the control group.

Participants included in the review
Patients with dementia (including patients with mild to moderate Alzheimer's disease of vascular dementia).

Outcomes assessed in the review
Global function, cognitive function and activities of daily living measured using primary and secondary outcome measures. The primary outcome measures were: the Gottfries-Brane-Steen (GBS) scale, the Clinical Global Impression (CGI), and the Syndrome Short Test (SKT). The secondary outcome measures were the Mini Mental State Examination (MMSE), Nurnburger-Alters-Beobachtungs-Skala (NAB), Zerssen Adjective Mood Scale (BfS: Befindlichkeitsskala) and Digit Symbol Substitution Test (DSST).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for review, or how many of the authors performed the selection.

Assessment of study quality
No formal assessment of quality was undertaken.

Data extraction
The authors do not state who, or how many of the reviewers performed the data extraction. Some of the data in this review was extracted from other reviews rather than directly from the original studies themselves.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
The authors do not state that any differences between the studies were investigated.
Results of the review
Eight RCTs were included in the review with 2,433 participants.

In the pilot study, statistically significant results were reported, in which patients treated with propentofylline did better, compared with those on placebo in respect of the measures of metabolic function. For the neuropsychological measures, the MMSE and DSST showed a trend improvement for those on propentofylline versus placebo which was not statistically significant, whilst the fragmented picture test showed a statistically significant improvement (p<0.05).

The second study (a Phase II study) found that the GBS and MMSE scores improved over three months for both treatment and placebo groups but the improvement was greater in the propentofylline group. The difference in improvement in GBS score ranged between 4 and 16 for different MMSE sub-groups on a scale of 156. The difference in improvement in MMSE was 1.3 on a scale of 30. Both these differences were statistically significant, but modest, and the clinical relevance is very doubtful. No benefits in terms of the psychometric assessments between the two groups were found and, thus, the efficacy of propentofylline as defined a priori was not demonstrated. In the RCT and 2 meta-analyses, the results are reported under the outcomes of global function, cognitive function, activities of daily living, and adverse events. Global function showed a slight improvement between baseline and 12 months for the propentofylline group and a decline for the placebo group over the same period. The difference in mean change from baseline was statistically significantly in the RCT and 1 meta-analysis. The treatment group showed greater improvement in condition at all points using the CGI score and the RCT (using the CGI score) reported a clinically relevant difference of -0.9 (plus/minus 1.1) at 12 months, but this was not statistically significant. Cognitive function (using mean SKT score) in the RCT showed an improvement for both groups at 3 months. The improvement was maintained in the propentofylline group at 12 months but the placebo group declined to baseline levels. The difference in mean change from baseline at 12 months was statistically significant in both the RCT (-1.4 plus/minus 1.0) and the meta-analysis (-0.8 plus/minus 0.5). In the RCT the mean total MMSE score for the propentofylline group showed an improvement between baseline and 12 months, and the placebo group showed a decline in condition over the same period. The difference in mean change from baseline was statistically significant in both the RCT (1.2 plus/minus 1.1) and the meta-analysis (0.7 plus/minus 0.5). In activities of Daily Living, the mean total NAB score from the RCT for both treatment groups showed a decline in condition throughout the course of the study, but was greater in the placebo group. The difference in mean change from baseline was statistically significant in both the RCT (-1.2 plus/minus 1.0) and the meta-analysis (-0.4 plus/minus 0.4). Adverse events reported were similar to those with the use of donepezil with 40% reported for the intervention group and 22% in the placebo group. Specific adverse events reported were: 1. Nausea (10% versus 4% in the placebo group). 2. Dizziness (9% versus 4% in the placebo group). 3. Headache (7% versus 3% in the placebo group). 4. Gastrointestinal pain (5% versus 2% in the placebo group).

Cost information
Modelling of the economic impact of drug therapy has been undertaken and shows a benefit in favour of propentofylline however this modelling is based on an assumed relationship between small changes in cognitive function and care requirement, which is not supported by firm evidence or by independent clinical expert judgement.

Authors' conclusions
The authors state that the trials showed very modest improvements in global function, cognitive function and activities of daily living. The improvements were statistically significant, but of very doubtful clinical relevance. The precise mode if action is as yet uncertain. However, the eight week withdrawal study suggests that the effects may be sustained following withdrawal, which would support the proposition that the drug may prevent disease progression rather than just provide symptomatic benefit.

CRD commentary
The authors have clearly stated their research question but not their inclusion and exclusion criteria. Details of the literature search are reported but it is not possible to determine whether the authors may have missed additional relevant studies. Search dates were not provided.

The quality of the included studies was not formally assessed and the authors have not reported on how the articles were selected, or how many of the reviewers were involved in the data selection and extraction.
The data extraction is reported in tables and text and the lack of pooling was appropriate however the authors have not stated their methodological reasoning for not pooling the data. There were no tests for heterogeneity and the authors have discussed their concerns about the methodological and data limitations of the review.

The authors’ conclusions appear to follow from the results but should be viewed with caution because of the many stated limitations of the review.

**Implications of the review for practice and research**

Practice: The authors do not state any implications for practice.

Research: The authors state that further research is required to:

1. Examine the costs and consequences of the use of propentofylline, especially to determine whether there is any reduction in the use of hospital, nursing home or community care services.

2. Determine the impact on the health and quality of life of carers (possibly using the Care Givers Activity Scale).

3. To develop validated and reliable assessment scales for measuring the quality of life of patients with dementia.

**Bibliographic details**


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**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.