WORKING GROUP ON ACUTE PURCHASING

A Review of the Use of Propentofylline in the Treatment of Dementia

January 1999

GUIDANCE NOTE FOR PURCHASERS 99/03

Series Editor: Nick Payne

InterDEC No. 04/1999

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 12 January 1999 at which this Guidance Note for Purchasers (in a draft form) was considered.

A REVIEW OF THE USE OF PROPENTOFYLLINE IN THE TREATMENT OF DEMENTIA

AUTHORS: Chilcott J, Perrett K, Golightly P, Sykes J, Whittingham M. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1998. Guidance Note for Purchasers: 99/03.

EXPERT ADVISORS TO TRENT DEC:
Mr J Chilcott, Senior Operational Research Analyst, ScHARR, The University of Sheffield.

(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: The Committee recommended that propentofylline should not be purchased, and agreed to review this position when further evidence on effectiveness, adverse reactions and cost becomes available.

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Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trusts Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst
Chairman, Trent Working Group on Acute Purchasing

ABBREVIATIONS

AD	Alzheimer's Disease
ADAS	Alzheimer's Disease Assessment Scale
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive sub scale
ADDTC	The State of California Alzheimer's Disease Diagnostic and Treatment Centre
BfS:Befinlichkeitsskala	Zerssen Adjective Mood Scale
cAMP	cyclic adenosine monophosphate
cGAMP	cyclic guanosine monophosphate
CGI	Clinical Global Impression
CIBIC plus	Clinician Interview Based Impression
CPMP	Committee for Proprietary Medicinal Products
CT	Computed Tomography
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Revised, Third Edition
DSMIV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSST	Digit Symbol Substitution Test
EMEA	European Medicines Evaluation Agency
EURODEM	European Commission for Concerted Action on the Epidemiology and Prevention of Dementia
GBS	Gottfries-Bråne-Steen scale
HMR	Hoechst Marion Roussel
ICD10	International Classification of Diseases, 10^{th} Edition
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NAB	Nürnburger-Alters-Beobachtungs-Skala
NGF	Nerve Growth Factor
NINDS-AIREN	The National Institute of Neurological Disorders and Stroke and European Panel of Experts
PET	Positron Emission Tomography
rCGMRGl	Regional cerebral glucose metabolism
RCTs	Randomised Controlled Trials
SKT	Syndrome Short Test

VaD	Vascular Dementia

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EXECUTIVE SUMMARY

It is estimated that the number of people with dementia in a 'typical' district health authority population of 500,000 is approximately 5,700, of whom around 3,000 are likely to have mild to moderate Alzheimer's disease or vascular dementia.

Propentofylline is the first of the new dementia drugs to have sought an approval for use in dementia of vascular origin, although this may be due to lack of studies with other drugs rather than a specific pharmacological action of propentofylline. On 20 October 1998 the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA) voted not to recommend marketing authorisation in the European Union. It is unclear whether an appeals procedure will be invoked but, in any case, it is now unlikely that this product will come to market before the end of 1999. The potential cost of propentofylline in the UK has not yet been released, however, an economic impact model for Sweden at 1991 prices, authored by pharmaceutical company employees, indicated a target price in the region of £350 per patient per year. Thus, if all potential patients received therapy, this would indicate a total cost to a health authority of around £1.1 million.

Evidence of efficacy is based on one published randomised controlled trial of 260 patients together with two published meta-analyses of the Phase III programme. The Phase III programme includes three further unpublished trials, bringing the total number of trial patients up to 1,273. Several assessment scales were reported in the trials; these addressed global function, cognitive function and activities of daily living. The Phase III programme was initiated before the widespread availability of the Alzheimer's Disease Assessment Scale (ADAS), and the scales used in the trials are not widely used or widely known in the UK. The trials examined the effects of propentofylline over a 12 month period and an eight week extension study examined the response to withdrawal.

The results of 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 quality of life for patients or carers was not examined in the trials. It should be recognised that quality of life assessment instruments have not yet been validated in this patient group.

The precise mode of action is, as yet, uncertain. However, the eight week withdrawal study, referred to above, 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.

The total cost includes the cost of the drug and the cost of a potential increase in demand for specialist assessment and diagnosis. There is no empirical evidence to suggest that drug therapy would result in a delay to the progression of the disease and thereby lead to savings in the NHS or other agencies. Modelling of the economic impact of drug therapy has been undertaken and shows a benefit in favour of propentofylline. This modelling, however, 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.

1. INTRODUCTION

This Guidance Note for propentofylline is the second in a series of evaluations of new drugs in dementia. The manufacturer of propentofylline is Hoechst Marion Roussel (HMR) and the proposed trade name is ViviQ. Parts of the report draw heavily on an earlier review of donepezil[1] but, for completeness, are repeated here in full.

It should be noted that propentofylline has been described as indicated for both vascular dementia (VaD) and Alzheimer's disease (AD); the potential target population is, therefore, larger than for donepezil, which is licensed specifically for AD.

1.1 Incidence and Pathology

Overall, dementia is a major cause of disability amongst older adults. It affects about 8% of people over 65 years of age, rising to over 20% in the over 80s. Approximately 70% of cases of dementia are due to AD and a further 20% fall into the category of VaD; 60% of all cases have mild to moderate disease.

The most recent compilation of prevalence data for dementia comes from the work of EURODEM,[2] the European Commission for Concerted Action on the Epidemiology and Prevention of Dementia. EURODEM has published age and sex specific prevalence estimates for dementia derived from 12 European population-based studies conducted or published since 1980. These studies have all had sample sizes sufficiently large to enable age and sex specific estimates of prevalence to be calculated with some precision.

The prevalence rate for dementia from the EURODEM study implies that there would be approximately 5,725 cases of dementia in a 'typical' district of 500,000 population, see Table 1. Assuming that AD is responsible for approximately 70% and vascular dementia for 20% of dementia cases in older adults, we would expect about 3,100 cases of mild and moderate disease which might be suitable for treatment with propentofylline.

Table 1 The Prevalence of Dementia Applied to a Population of 500,000

Age Group	Population	Prevalence of Dementia Male	Female	Expected Dementia	Mild and Moderate AD	Mild and Moderate VaD	Mild and Moderate Total
45-64	112,756	0.1%	0.1%	68	28	8	37
65-69	24,184	2.2%	1.1%	393	165	47	212
70-74	22,022	4.6%	3.9%	928	390	111	501
75-79	15,056	5.0%	6.7%	906	380	109	489
80-84	10,838	12.1%	13.5%	1,411	592	169	762
85+	8,079	21.5%	26.2%	2,020	849	242	1091
Total 45+	192,935			5,725	2,405	687	3,092
All ages	500,000						

The incidence rate of new cases of dementia is estimated to be 1% per annum in people aged 65 or over, and increases with age. It would be expected that there would be 800 new cases of dementia in the 'typical' district each year, with about 560 and 160 of these being of the Alzheimer's and vascular types respectively.

1.2 Prognosis and Mortality

Originally, all dementia was thought to be caused by vascular lesions. However, senile dementia of the Alzheimer's type, is now generally considered to be distinct from VaD. Histopathological studies indicate that vascular pathology is the sole cause of symptoms in 9-33% of patients with dementia and contributes to dementia in a further 10-36% of cases. Vascular dementia is probably the second commonest type of dementia after AD, and may be the commonest type in patients over the age of 85.

It was once thought that cerebro-arteriosclerotic changes were the fundamental lesions until Hachinski,[3] in 1994, concluded that when VaD was responsible for dementia it was not directly the result of cerebral arteriosclerosis, but as a result of multiple infarcts, secondary to embolic disease from extra-cranial arteries and the heart. Therefore, the term multi-infarct dementia was adopted. It has been realised since that ischaemic lesions can occur without evidence of infarction and that, in some cases, haemorrhage is the important mechanism. It has also been shown that ischaemia of the sub-cortical white matter may be the commonest mechanism. The white matter is especially vulnerable, because it is supplied by long penetrating end arterioles from the surface and base of the brain. Initially, it was thought that the quantity of cerebral softening (indicative of ischaemia) proportionally

accorded with the severity of the dementia with a threshold effect apparent. It has since been shown that a single strategically sited lesion, for example, in the inferior parietal lobe, can cause dementia. Stroke and age are the most important risk factors for VaD and a symptomatic stroke increases the risk of dementia more than nine-fold.

The term Vascular Dementia has been adopted by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV), whilst in the 10th edition of the International Classification of Diseases (ICD10), VaD is sub-classified into VaD of acute onset, multi-infarct dementia, sub-cortical VaD and mixed or unspecified types.

The Hachinski lschaemic Scale is widely used for research purposes. VaD is diagnosed when the patient is given a score of seven or higher. The scale has poor inter-rater reliability and modified versions have been proposed.

More recently, two new sets of criteria have been formulated by:

- The State of California Alzheimer's Disease Diagnostic and Treatment Centre (ADDTC);

- The National Institute of Neurological Disorders and Stroke and European Panel of Experts (NINDS - AIREN).

Both require the presence of:

- dementia;

- cerebrovascular disease;

- a relation between the two.

These scales may be more sensitive than the Hachinski Scale, although validation studies on post mortem examinations are awaited. All the above are based on the multi-infarct concept of VaD, except for the ICD10 and the NINDS-AIREN.

Pathologically, atrophy and ventricular enlargement is seen as in AD, but with the additional changes of cerebral softening due to intercranial infarcts and haemorrhages. These

changes can be seen in vivo on a Computed Tomography (CT) scan and more clearly on a Magnetic Resonance Imaging (MRI) scan, which may also show white matter lesions more clearly.

Positron emission tomography (PET) shows functional as opposed to morphological changes. It can distinguish multi-infarct dementia from AD by showing a characteristic area of hypo-metabolism.

Once the diagnosis of VaD has been made, special attention should be given to:

- detection of vascular risk factors, including hypertension and diabetes;

- examination of the cardiovascular system, with particular regard to the causes of thromboembolism, including atrial fibrillation, valvular heart disease and carotid stenosis;

- exclusion of other treatable causes of dementia, such as, endocrine disorders and vitamin deficiencies.

Treatment is aimed at reducing the risk of further damage by the treatment of associated cardiovascular disease, and prophylaxis against thrombosis by the use of anti-platelet drugs and anticoagulants. Treatment of hypercholesterolaemia and advice and support about stopping smoking is also important. Those with substantial carotid stenosis should be considered for surgery. Patients with vasculitis may benefit from immuno-suppressive drugs. Previously, neuro-metabolic treatments have not been shown to be clinically useful.

Symptomatic treatments such as tranquillisers and hypnotics often have to be considered and depression is common, probably because insight is often retained. Therefore, antidepressants are commonly used.

The course and survival rate in VaD are much less predictable than in AD with potentially great individual variability. The onset is typically abrupt followed by a stepwise and fluctuating course, and is characterised by rapid changes in functioning rather than slow progression. However, an insidious onset with gradual decline, associated with ‘silent’ infarcts, may also be encountered. Treatment of hypertension and other risk factors may alter the course and prevent further progression. Comparative studies have found a slightly better two year survival average than in AD, but five year studies have not shown a

significant difference. There may be slightly better prospects for females. Death is commonly attributed to ischaemic heart disease. In VaD, focal neurological signs are often present, in association with other evidence of VaD. This can be contrasted with the insidious and gradual onset of dementia in AD, which is characterised by a more consistent and widespread impairment consisting of amnesia, dysphasia, dyspraxia and agnosia. The course of AD tends to be slowly progressive with, for example, a deterioration of three - four points per year on the serial Mini Mental State Examination (MMSE). The average duration of illness from onset of symptoms to death is eight to ten years. Although, clinicians have reported cases of AD which appear to plateau for significant periods of time, this is not characteristic. Unfortunately, post-mortem validation of such cases is not often pursued. Therefore, for clinical purposes, a patient in whom the course of the dementia is not progressive should not be considered to have AD. Females with AD tend to survive longer following diagnosis, but the reason for this is open to speculation. It may be that male demented patients tend to be in relatively poorer physical condition generally. Most people with severe AD die of intercurrent illness, particularly broncho-pneumonia. However, some patients seem to 'fade away' over a period of several weeks without any specific reason being found at post-mortem other than AD.

1.3 The Mode of Action of Propentofylline

Propentofylline has a different pharmacological basis for use in dementia than the two existing drugs, donepezil and rivastigmine. The latter are both cholinesterase inhibitors, which have predominantly central effects with limited peripheral activity, hence minimising toxicity. Other drugs yet to reach the market, in the UK or elsewhere, are likely to have various pharmacological activities; these are summarised in Table 2 below.

Table 2 Summary of New Drugs in Dementia and their Modes of Action

Propentofylline	Phosphodiesterase inhibitor Adenosine re-uptake inhibitor
Galantamine	Cholinesterase inhibitor
Metriphonate	Cholinesterase inhibitor
Milameline	Muscarinic receptor antagonist
Nefiracetam	GABA receptor antagonist
Sabeluzole	Calcium channel antagonist
Xanomeline	Muscarinic M1 & M4 antagonist

Propentofylline, however, is a phosphodiesterase inhibitor (c.f. theophylline, caffeine) and an adenosine re-uptake inhibitor. The relative and absolute significance of these activities in dementia is not fully substantiated. It appears to limit the action of glial cells in the brain by preventing the enzymatic breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) through inhibition of cyclic nucleotide phosphodiesterases. cAMP and cGMP are thought to have important roles in the regulation of neural function. Propentofylline also limits the re-uptake of adenosine, resulting in extracellular accumulation, which is considered to potentiate its neuroprotective effects mediated by adenosine A1 and A2 receptors.[4]

There is also some evidence that propentofylline reduces neuronal damage caused by ischaemia and inhibits potentially neurotoxic properties of activated microglial cells. It may also promote brain tissue repair by enhancing the synthesis and release of neurotrophin nerve growth factor (NGF) from astroglial cells and increase NGF content in the aged brain.[4]

1.4 Scale of Problem in a 'Typical' District

A prevalence of approximately 3,100 cases of mild to moderate dementia would be expected in a 'typical' district health authority population of 500,000. The price of propentofylline in the UK has not as yet been released. However, an economic evaluation[5] undertaken by employees of HMR, set in Sweden and priced at 1991 levels, quotes a daily price of SEK13; this would indicate a very approximate price of £1 per day. On this basis, the annual cost of treatment per patient might be expected to be around £350. Thus, if all potential patients in a district are treated, then the total annual cost of treatment to the district would be in the region of £1.1million.

2. USE OF PROPENTOFYLLINE IN THE TREATMENT OF DEMENTIA: SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Available Evidence

Eight randomised controlled trials (RCTs), which address the clinical effectiveness of propentofylline, have been identified through a systematic search of the published and grey literature. The trials are summarised in Table 3.

Table 3 Randomised Controlled Trials of Propentofylline

Trial	Number in Study	Lead Author	Publication Status	
Pilot study	30	Mielke R	Published[6,7]	
Phase II	190	Moller HJ	Published[8]	
Phase III - Study I	293	--	Unpublished	Included in 'meta-analyses' by Kittner[10] & Rother[11]
Phase III - Study II	260	Marcusson J	Published[9]	
Phase III - Study III	170	--	Unpublished	
Phase III - Study IV	550	(Karlsson et al.)	Unpublished	
Study 304 (AD)	486	Rother M	Conference poster[12]	
Study 305 (VaD)	454	Pischel T	Conference poster[13]	

The Phase III trial reported by Marcusson[9] is included in the Kittner 'meta-analysis',[10] and also the Rother paper,[11] where it is referenced. This, therefore, leaves three further Phase III trials which have not been fully published. Full details of inclusion and exclusion criteria, drop-outs and adverse events from each of the trials are not available from the meta-analyses. These issues mean that it is impossible adequately to critically appraise the meta-analyses, as details of three of the four trials have to be taken on trust; the results and the conclusions drawn from the analyses must, therefore, be open to question.

A literature search was undertaken, based on the medical and health databases: including MEDLINE; EMBASE; HEALTHSTAR, the Cochrane Collaboration Trials Register, the NHS CRD DARE database and the NHS Economic Evaluation database, together with examination of the relevant health technology assessment agency resources: such as, web sites and booklets. Search terms were based on 'propentofylline', 'HWA285' and the CAS registry number.

2.2 Outcome Measures

The Phase III trials used a battery of tests and assessment scales. The primary outcome measures are the Gottfries-Bråne-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), Nürnburger-Alters-Beobachtungs-Skala (NAB), Zerssen Adjective Mood Scale (BfS: Befindlichkeitsskala) and Digit Symbol Substitution Test (DSST). With the exception of the MMSE, these are not widely used assessment scales and are not in active use within the Trent Region or the UK in general. It is not possible to comment on their clinical relevance, other than by reference to the published literature. Therefore, a brief introduction to the scales is included below, based on either original publications or on background information given in the Marcusson paper.[9]

The two trials detailed in the poster presentations to the International Conference on Alzheimer's Disease and Related Disorders[12,13] use the more widely known and accepted Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-cog) and the Clinician Interview Based Impression (CIBIC plus) assessment scales.

Primary Outcome Variables in the Phase III trials

1. The *Gottfries-Bråne-Steen (GBS)*[14] scale uses a 7-step scoring system to measure motor function, intellectual function, emotional function and additional symptoms. The score ranges from 0 to 156 points and an increase indicates a deterioration in condition.

2. The *Clinical Global Impression (CGI)* scale comprises two items each measured on a scale from 0 to 7 points. Item I measures severity of illness and item II measures global improvement compared to the previous assessment - note that only item II is

used in the primary efficacy measure. An increase in score indicates a deterioration in condition.

3. The *Syndrome Short Test (SKT; Syndrom Kurztest)*[15] measures impairment of memory, attention, speech and mental agility by means of a 4-step scoring system which is standardised for age and premorbid IQ. Parallel forms are used to avoid learning effects. The total score ranges from 0 to 27 points where an increase in score indicates a deterioration in condition.

Secondary Outcome Variables in the Phase III Trials

1. The *Mini Mental State Examination (MMSE)*[16] is a well established measure for distinguishing between organic and functional illness in older adults. It shows good inter-rater and test-retest reliability. The MMSE is more sensitive than alternative measures at milder levels of disability, but is subject to sociodemographic bias. Scores between 10 and 26 correspond to mild to moderate dementia.

2. The *Nürnburger-Alters-Beobachtungs-Skala (NAB)* is a measure of a patient's performance at activities of daily living. The assessment exercise is completed by the patient's carer and comprises 15 items, each measured on a 3 point scale. The scores range from 15 to 45 and an increase in score indicates a deterioration.

3. The *Zerssen Adjective Mood Scale (BfS: Befindlichkeitsskala)* evaluates treatment induced changes of moods and is completed by the patient. The total score ranges from 0 to 56 where an increase indicates a deterioration. This scale is of particular interest given the high incidence of depression referred to earlier.

4. The *Digit Symbol Substitution Test (DSST)* measures cognitive performance by asking the patient to copy fixed combinations of numbers and symbols. The sum of correct answers obtained within 90 seconds gives the score, subject to a maximum of 67; parallel forms being used throughout the study to avoid learning effects. A score decrease indicates a deterioration.

Other Scales Used

1. The *Alzheimer's Disease Assessment Scale*[17] *- cognitive subscale (ADAS-cog)*. This is an 11 point subscale of the ADAS with a maximum score of 70 (most severe). The ADAS-cog measures memory, orientation, attention, language and motor skills, but not everyday living skills. Although the scale shows good inter-rater and test/re-test reliability, it has been described as 'too sensitive to change'[18] and not conveying a sense of clinical relevance. In research terms, a difference of four points on the ADAS-cog is seen as significant. Seven points will show up as slight clinical improvement (e.g. patient recall is slightly better, a patient being able to name a few more objects). The overall rate of decline in patients with AD is between 6 and 12 points per year. Deterioration is not necessarily linear and there may be marked variation between individuals depending on initial severity.

2. A revised version of the *Clinician Interview Based Impression*[18] *(CIBIC plus)*. This was used by experienced clinicians independently of the ADAS-cog. The measure includes caregiver interview information as well as patient assessment. The CIBIC plus is a seven point scale which measures a patient's global performance in cognitive, behavioural and functional terms and incorporates input from the primary caregiver. The test/re-test reliability of CIBIC plus is poor, although reliability is an issue for all subjective measurements.

2.3 Pilot and Phase II Studies

The pilot study, reported by Mielke et al.,[6] was primarily aimed at assessing the effects of propentofylline on the regional cerebral glucose metabolism (rCGMRGI) of patients with VaD over a three month period. The trial was double-blind, placebo controlled and randomised. Patients, aged between 40 and 85, with a clinical diagnosis of VaD according to the Diagnostic and Statistical Manual of Mental Disorders, Revised, Third Edition (DSM-III-R), were included in the trial. Patients were mildly to moderately demented with an Hachinski score of seven or more and MMSE greater than 15 and less than 25. Clinical treatment effects were assessed as secondary outcomes, using the MMSE, the memory task, the Digit Symbol Subtest (DSST) and the fragmented picture task. 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 Phase II study[8] was a three month multi-centre, double blind, placebo controlled parallel group trial, aimed at assessing the effects of propentofylline on cognition or disease progression. The primary efficacy measure was defined as improved performance on the GBS scale and improvement in at least two of eight psychometric tests. Patients aged 55 to 80, with a diagnosis of dementia according to the DSM-III-R were included in the trial. Patients were mildly to moderately demented with MMSE greater than 15 and less than 25 and a maximum GBS score of 14. The GBS and MMSE scores improved over three months for both treatment and placebo groups, the improvement, however, 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 are 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.

2.4 Results of Phase III Trials

Three papers have been published from the Phase III programme, one trial report, Marcusson[9], and two meta-analyses, Kittner[10] and Rother.[11]

The paper by Marcusson et al. details a study of 260 patients in 19 centres across seven European countries[9]. Generally speaking, it appears to be a well conducted study which is clearly written and merits serious consideration. The methods section details the different scoring systems used in the trials, together with background references. This is of particular importance since the measures appear to be obscure. Furthermore, clinically relevant score differences are defined *a priori* for each of the measures.

The paper by Kittner, Rössner and Rother,[10] all drug company employees, is a 'meta-analysis' of four unreferenced studies. There are a number of methodological criticisms of this paper. The statistical convention when undertaking a meta-analysis of several trials is to pool the results, e.g. in terms of odds ratio or relative risk from the individual trials, thus allowing the final summary measure to be weighted according to the size and variability from

the individual studies. The analysis presented in the Kittner paper essentially ignores the separate studies, does not test for homogeneity of the studies, and effectively pools all patients into one big trial; this gives equal weight to all studies and is not considered good practice.[19]

The number of patients excluded and the details of the exclusion criteria in each of the trials is not given. The paper states that 'patients with at least one post baseline assessment per variable are included in each analysis'. It is unclear whether or not this contradicts the statement that the analysis was on an intention to treat basis. The paper claims clinically relevant treatment differences, but does not define these *a priori*. A sub-group analysis is undertaken for patients with AD and VaD, but it should be noted that the classification of these conditions is inconsistent between the four trials. Specifically, the Hachinski scale provides a narrower definition of multi-infarct dementia whilst the NINDS-AIREN classification also includes single infarct and acute onset dementias.

The paper by Rother et al.[11] presents a review of the Phase III programme, references the trial reported by Marcusson et al. and confirms the remaining three trials as unpublished. The sub-group analysis for VaD and AD is repeated. Additional details of one of the subject trials, ascribed to Karlsson et al., are given, and an eight week withdrawal study undertaken as an extension to this trial is discussed and results presented. The analysis in this paper is subject to the same methodological criticisms as the Kittner analysis.

The available information on the four studies within the Phase III programme is summarised in Table 4.

Table 4 Summary of the Phase III Programme

TRIAL	European Propentofylline Study Group[9] - Meta-analysis Study II[10]	Karlsson (Unpublished) - Meta-analysis Study IV[10]	Meta-analysis Study I[10]	Meta-analysis Study III[10]
DATE	1991- 93	1994-96	Unknown	Unknown
DESIGN	Multinational, randomised, placebo controlled, double-blind trial	Multinational, double-blind, placebo controlled, randomised	Double-blind, placebo controlled, randomised	
PATIENT NUMBERS	260 patients 129 propentofylline 131 placebo	550 patients 265 propentofylline 285 placebo	293 patients	170 patients
INCLUSION CRITERIA	Mild to moderate AD or VaD (DSM-III-R). MMSE 15–25, dementia present for at least 6 months.			
Classification: **Alzheimer's disease** **Vascular dementia**	DSM-III-R Hachinski score	NINCDS/ADRDA NINDS/AIREN	DSM-III-R Hachinski score	NINCDS/ADRDA NINDS/AIREN
EXCLUSION CRITERIA	Other significant medical conditions; history of psychiatric, neurological and/or other cerebral diseases; concomitant treatment to improve cerebral blood flow which could not be stopped prior to screening; participation in another clinical trial within 3 months of study.	Secondary dementia, previous and concomitant diseases and medications interfering with diagnosis or interpretation of results. Limited details only are available from the Meta-analysis.[9]		
DOSAGE	3 x 300 mg daily			
PRIMARY EFFICACY VARIABLES	GBS (clinician), CGI global change (clinician), SKT (psychologist).			
SECONDARY ENDPOINTS	MMSE, DSST, NAB, BfS	MMSE (clinician), NAB (caregiver)		
STUDY DURATION	3 months washout 12 months treatment	48 weeks 8 weeks withdrawal phase	6 months	12 months
WITHDRAWAL AND ADVERSE EVENTS	305 patients screened, 44 excluded. 1 patient randomised to propentofylline, but did not take medication.	Number of patients excluded not available.		
	Propentofylline / Placebo	Overall - Propentofylline / Placebo		
Total withdrawal	43/130 (33%) / 30/131 (22%)	25% / 19%		
Due to adverse events	11/130 (8%) / 5/131 (3%)	N/A / N/A		

Global function

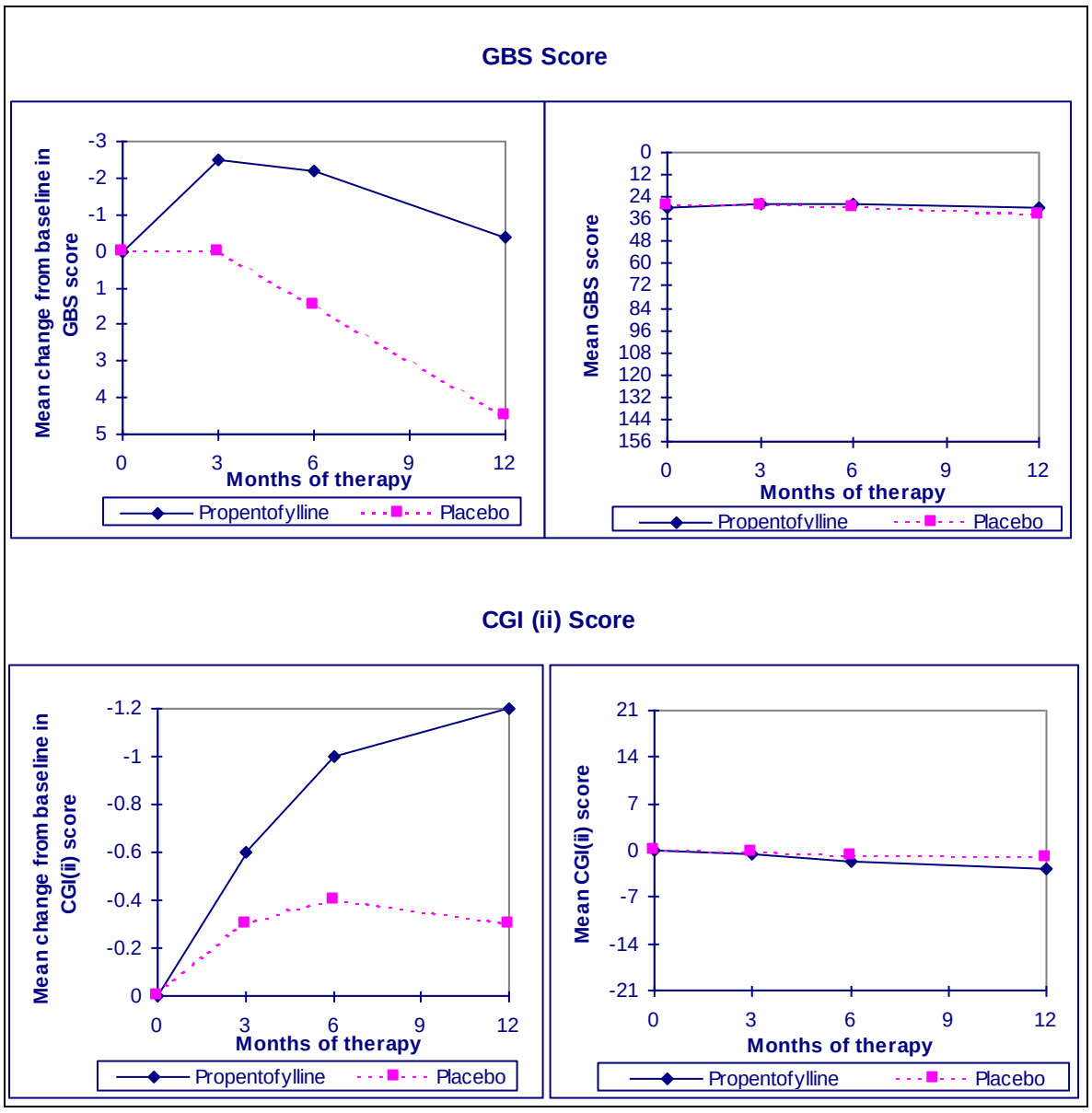
From the Marcusson trial,[9] the mean total GBS score for the propentofylline group showed a slight improvement between baseline and 12 months; the placebo group, however, showed a decline in condition over the same period, see Figure 1. The difference in mean change from baseline was statistically significant in both the Marcusson trial and the meta-analysis, see Table 5. The Marcusson trial alone showed a difference of -4.9 (±3.8), whereas the meta-analysis showed a difference of only -2.5 (±1.5). These are both less than the clinically relevant difference of six points quoted in the Marcusson paper. The magnitude of the change relative to the full range of the scale is also highlighted in Figure 1.

The CGI (item ii) score measures the change in global function since the previous visit. The Kittner meta-analysis, however, only gives the difference in scores for each patient group. In the Marcusson trial, both the propentofylline and placebo group showed an improvement in condition between each visit. However, the treatment group showed greater improvements at all points, see Figure 1. The meta-analysis claimed a statistically significant change in scores of -0.2 (±0.2) at the three and six month points and a change of -0.4 (±0.2) at 12 months. See Table 5. These are all less than the clinically relevant difference of 0.5 points quoted in the Marcusson trial. The Marcusson trial did show a clinically relevant change of -0.9 (±1.1) at 12 months, but this was not statistically significant. The magnitude of this change relative to the full range of the scale is also highlighted in Figure 1.

Cognitive function

The mean total SKT score, from the Marcusson trial,[9] for both groups showed an improvement at the three month timepoint. This improvement was maintained in the propentofylline group at 12 months, whilst the placebo group declined to the baseline levels; see Figure 2. The difference in mean change from baseline at 12 months was statistically significant in both the Marcusson trial and the meta-analysis. The Marcusson trial showed a difference of -1.4 (±1.0), whereas the meta-analysis showed a difference of -0.8 (±0.5). See Table 4. These are both less than the clinically relevant difference of four points quoted in the Marcusson trial. As before, the magnitude of the change relative to the full range of the scale is highlighted in Figure 2.

Figure 1 Effect of Propentofylline on Global Function (data from Marcusson[9])



Notes:

1. The results are from the Marcusson trial and in all cases the benefits in favour of propentofylline were greater than the benefits shown in the meta-analyses.
2. The graphs on the left show the mean change from baseline for the placebo and propentofylline patient groups, for the two scales.
3. The graphs on the right show how the changes in score over the trial period compare with the overall range of the assessment scales.
4. The CGI(ii) scale has a range of 0-7 for the change between visits - thus the range of achievable change over three visits is 21 points.

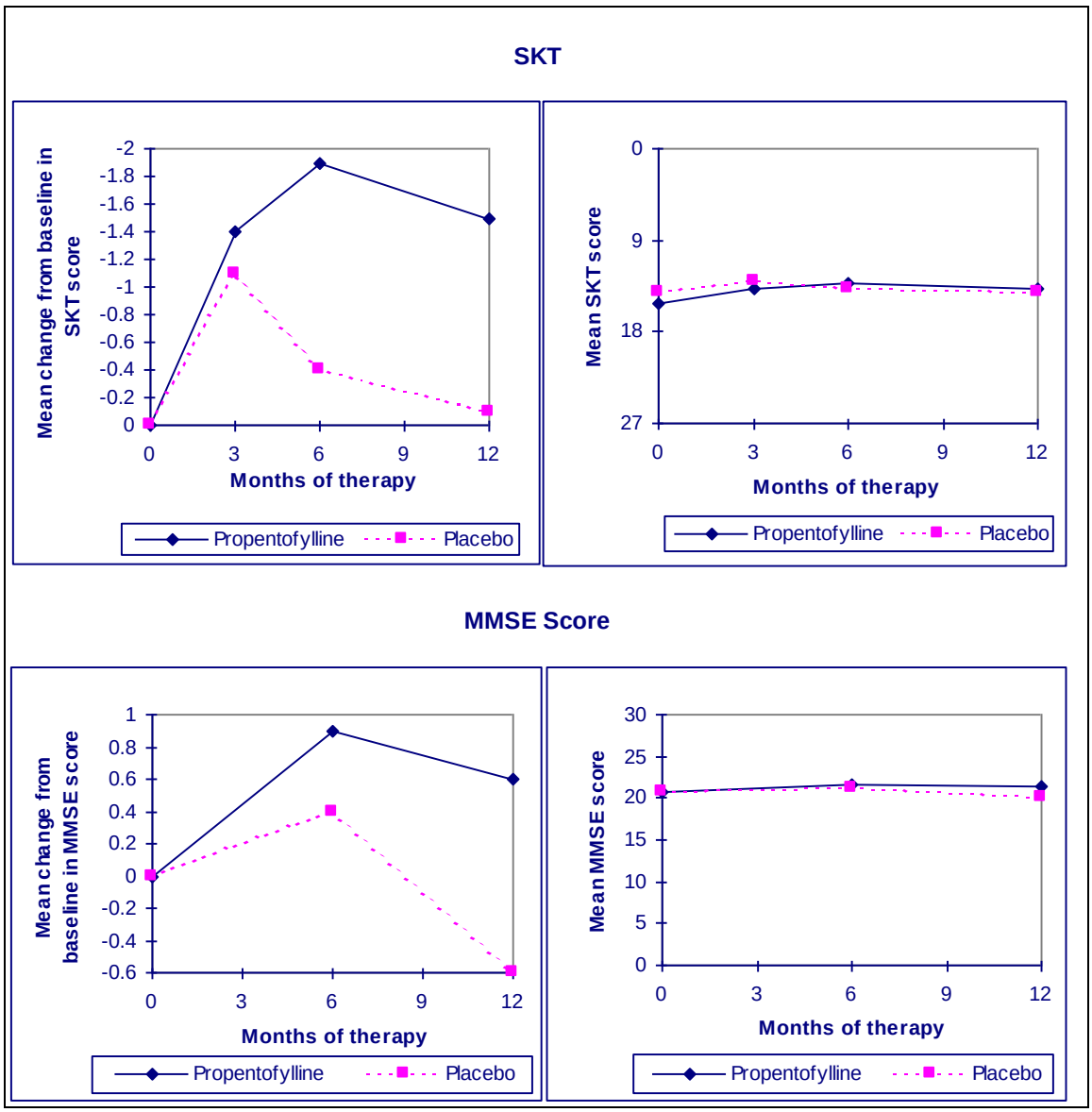
The SKT measure has been reported to correlate well with the ADAS-cog assessment scale.[15] A treatment difference of 1.7 on the SKT scale is quoted as being equivalent to a change of 3.4 points on the ADAS-cog scale. In addition, the results from the two studies reported in the conference posters[12,13] showed a difference of approximately 1.5 points on the ADAS-cog scale. As mentioned above, a difference of four points on the ADAS-cog scale has been defined as significant in research terms and a change of seven points would show up as a slight clinical improvement.

From the Marcusson trial, the mean total MMSE score for the propentofylline group showed an improvement between baseline and 12 months. However, the placebo group showed a decline in condition over the same period; see Figure 2. The difference in mean change from baseline was statistically significant in both the Marcusson trial and the meta-analysis. The Marcusson trial showed a difference of 1.2 (±1.1), whereas the meta-analysis showed a difference of 0.7 (±0.5); see Table 5. The magnitude of the change relative to the full range of the scale is highlighted in Figure 2.

Activities of Daily Living

The mean total NAB score, from the Marcusson trial, for both treatment groups showed a decline in condition throughout the course of the study, see Figure 3. The deterioration was greater, however, in the placebo group. The difference in mean change from baseline was statistically significant in both the Marcusson trial and the meta-analysis. The Marcusson trial showed a difference of -1.2 (±1.0), whereas the meta-analysis showed a difference of only -0.4 (±0.4).

Figure 2 Effect of Propentofylline on Cognitive Function (data from Marcusson[9])



Notes:

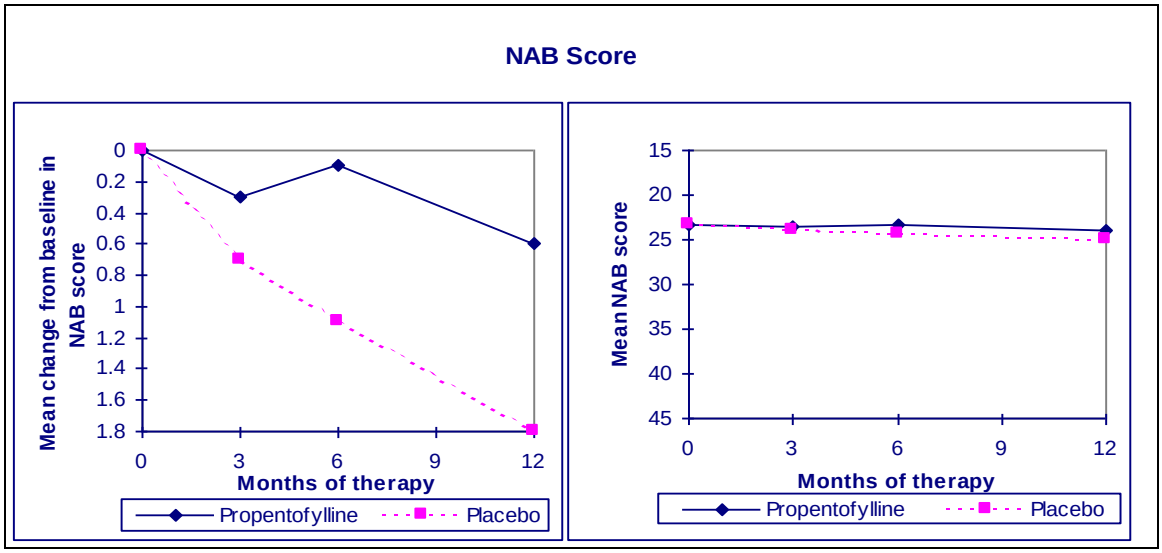
1. The results are from the Marcusson trial and in all cases the benefits in favour of propentofylline were greater than the benefits shown in the meta-analyses.
2. The graphs on the left show the mean change from baseline for the placebo and propentofylline patient groups, for the two scales.
3. The graphs on the right show how the changes in score over the trial period compare with the overall range of the assessment scales.

Table 5 **Difference in Change (propentofylline versus placebo) from Baseline at Final Visit (12 months / 48weeks)**

	Score Range	Disease Progression	Clinically Relevant Difference	Meta Analysis Kittner	p	EPSG Marcusson	p
Population				1,273		260	
GBS *Clinician*	0 - 156	Increase	6	-2.5 (-4.1, -1)	***	-4.9 (-8.6, -1)	***
CGI (ii) *Clinician*	0 - 7	Increase	0.5	-0.4 (-0.6, -0.2)	***	-0.9 (-2, 0.3)	NS
SKT *Psychologist*	0 - 27	Increase	4	-0.8 (-1.3, -0.3)	***	-1.4 (-2.4, -0.4)	**
MMSE *Clinician*	0 - 30	Decrease		0.7 (0.2, 1.3)	***	1.2 (0.1, 2.3)	***
NAB *Clinician*	15 - 45	Increase		-0.4 (-0.8, 0.1)	**	-1.2 (-2.2, -0.2)	**

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Figure 3 **Effect of Propentofylline on Activities of Daily Living (data from Marcusson[8])**



Notes:

1. The results are from the Marcusson trial and in all cases the benefits in favour of propentofylline were greater than the benefits shown in the meta-analyses.
2. The graphs on the left show the mean change from baseline for the placebo and propentofylline patient groups, for the two scales.
3. The graphs on the right show how the changes in score over the trial period compare with the overall range of the assessment scales.

2.5 Adverse Events

Propentofylline has been shown to be well tolerated, with a similar side-effects profile in both patients with AD or VaD. The side-effects reported were similar to those associated with the use of donepezil. The most frequently reported events were nausea, dizziness, headache, gastrointestinal pain, flushing, dyspepsia, vertigo, asthenia, loss of appetite, vomiting and hot flushes. These events were either associated with the pharmacological action of propentofylline on cerebral blood flow or are typical for xanthine derivatives. Adverse events were usually intercurrent and of short duration.[10] The principle adverse events are summarised in Table 6.

Table 6 Adverse Events in the Phase III Programme

	Propentofylline	**Placebo**
Adverse events	40%	22%
Nausea	10%	4%
Dizziness	9%	4%
Headache	7%	3%
Gastrointestinal pain	5%	2%

2.6 Conclusion on Direction of Evidence

The best quality published evidence arises from the Marcusson trial. This trial, by its own definition of *a priori* criteria, fails to prove clinically relevant efficacy of propentofylline.

The meta-analyses, Kittner and Rother,[10,11] provide poorer quality evidence by reason of their reliance on unpublished trial data. These meta-analyses do not give *a priori* definitions of criteria for clinical efficacy yet claim to prove not only statistically significant but also clinically relevant benefits. The benefits shown in each assessment scale are, however, small in comparison to the overall scale ranges and are lower than the clinically relevant differences defined in the Marcusson paper.

The conclusion is, therefore, that propentofylline appears to give a very modest benefit over a 12 month period in cognitive function, global function and in activities of daily living. These benefits may be statistically significant, but it is doubtful whether they are clinically relevant at the levels shown in the trials.

There is some evidence to indicate that these benefits, though marginal, may be sustained after withdrawal.[11] This would suggest that the mode of action of propentofylline is not purely symptomatic. Therefore, there may be potential for longer-term benefits, though further evidence is required.

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

3.1 Summary of Potential Costs and Benefits of Propentofylline

Benefits	**Disbenefits**
1. Very modest improvement in global function for patients with mild to moderate AD and VaD. 2. Very modest improvement in cognitive function. 3. Very modest improvement in activities of daily living. 4. Quality of life for patient:- no evidence available. 5. Quality of life for carers:- no evidence available. 6. Morbidity in carers:- no objective evidence available.	1. Side-effects from treatment. 2. Prolonged distress, especially when insight is preserved.
Savings	**Costs**
1. Possible savings made in the NHS (e.g. by delayed hospital entry) - no empirical evidence available. 2. Possible savings in reduced need for nursing/residential home care - no empirical evidence available. 3. Possible savings in other areas of society (e.g. reduction in benefits, reduction in home care required) - no empirical evidence available. 4. Increased earnings by patients or carers - no quantitative evidence available.	1. Cost of the drug Not known - possibly in the region of £350 per annum[5] @ 300mg 3 times daily. 2. Possible cost due to side-effects (hospitalisation, non-hospitalisation) - no evidence available. 3. Increased cost of diagnosis and assessment. 4. Increased costs arising from prolonged need for care.

3.2 Health Economic Studies of the New Drugs for Dementia

A number of health economic studies of the new dementia drugs, tacrine, donepezil and propentofylline have been published.[20,21] The papers do not constitute cost-effectiveness or cost-benefit studies. No mortality or quality of life benefits have been demonstrated to accrue from the use of the drugs, hence, the measures of cost per life year gained or cost per quality adjusted life year gained are not appropriate. The main thrust of these studies is to investigate the economic impact of introducing the drugs and to demonstrate that they could potentially be cost-neutral or cost-saving over conventional management strategies. In general, a similar approach is taken in each of these papers, although they vary in methodological detail. The approach is outlined below:

- The cost of caring for dementia patients in the different care settings is identified.

- The patients in the different care settings are profiled, at a point in time, in terms of some measure of disease progression. Most commonly this is cognitive function as measured by the MMSE.

- RCT evidence is used to show the effectiveness of the drug in relation to disease progression. This is usually in terms of the difference in mean change from baseline in MMSE score and is usually over a relatively short period of time.

- The long-term disease progression under conventional management is described in terms of the changes in MMSE over the course of the disease, either over an arbitrarily long time horizon or to death. The RCT evidence for the drug is then superimposed on this to model the long-term effects of drug therapy on MMSE progression.

- A causal relationship between cognitive function, as measured by the MMSE, and the care setting is then assumed. This is used as the basis for a model of long-term resource usage and costs. A linear regression model of cost against MMSE score is proposed in the propentofylline study, whilst a Markov, state transition model, is developed in the study on donepezil, and a decision analytic method is used in the tacrine study.

- The long-term care requirements and, thus, costs over the defined time period, are modelled for a cohort of patients starting with a range of MMSE scores and in a range of care settings with and without drug therapy.

3.3 Economic Impact of Introducing Propentofylline for the Treatment of Dementia in Sweden

The propentofylline study[5] claims to show that propentofylline will be cost saving when used in conjunction with conventional packages of care. These claimed savings result from delays in transition to more costly forms of care throughout the period of disease progression. These delays are assumed to arise as a result of the marginal benefits in cognitive function.

The baseline result claims an annual saving per patient ranging from SEK 5,500 to SEK 6,400 (approximately £370 to £430) over the first four years of treatment. This gives a total net saving per patient over the full duration of disease progression of approximately SEK 14,000 (£930). This is estimated to be 3.8% of care costs for mild to moderate dementia patients and 0.5% of the cost for all patients.

A one-way sensitivity analysis for model parameters is undertaken, supported by a number of scenario analyses which investigate the effects of varying some of the assumptions within the model. It should be noted that no multi-way sensitivity analysis has been undertaken to obtain an overall assessment of the effect of uncertainty within the model.

Accepting the assumptions within the model, the positive results are sensitive to variation in:

- efficacy of propentofylline, in terms of deterioration in MMSE prevented. (Note the lower 95% confidence interval of efficacy from the Kittner meta-analysis leads to a net cost increase from propentofylline);

- the regression model coefficients; that is the cost per one point change in MMSE;

- the assumption that mortality is not affected;

- the price of propentofylline.

The key to this paper, however, is the assumption of a causal relationship between cognitive function, as measured by the MMSE, and the resource usage or cost.

The paper takes a snapshot of the dementia population at a point in time and undertakes a linear regression analysis to investigate the relationship between MMSE score and cost. It finds that there is a correlation between cognitive function and the need for more intensive (and costly) care; that is, patients with more severe dementia need higher levels of support. The subsequent assumption that small variations in the MMSE will lead to corresponding changes in care requirements and, therefore, costs, is the weakest link in the argument and not supported by objective evidence or independent clinical judgement.

In order to show a benefit from drug treatment, it needs to be proved that the marginal cognitive benefit will affect the need for particular levels of care and that the transition between care settings will consequentially be delayed. In practice, the decision to move from, for example, home care to residential care or residential care to nursing care is determined by a large range of diverse factors both medical and social. These include:

- presence of a partner or other carer;
- mobility;
- ability to wash, dress and prepare food;
- availability of alternative support functions;
- level of confusion or cognitive function.

In addition, there is likely to be a high level of inertia against moving between care settings. Thus, for example, an existing patient who is living and being supported in his/her own home is likely to be maintained there for as long as possible, whereas a new patient presenting with similar symptoms may be referred to residential care.

On a more technical, but related note, the central concepts in this paper are the linear regression of MMSE and costs of care. The reporting of this modelling is incomplete, however:

- It is not clear from the methods or the results section of the paper what factors were considered for inclusion in the model. It reports only that sex was considered for inclusion, but did not improve the fit of the model. This implies that other potentially important factors, such as, the presence of a partner or other carer, mobility or activities of daily living were not considered.

- The regression method used - stepwise, forwards or backwards - was not reported.

- The quality of fit of the model is not adequately described, only the adjusted r^2 value being given. The r^2 statistic is 0.42 indicating that the MMSE score explains 42% of the variation in costs. Given the central role of the model, the F statistic for the MMSE score giving the statistical significance of this factor should be given. Furthermore, and perhaps more importantly, the testing of the linearity assumptions should be addressed explicitly.

With these reservations, the r^2 statistic indicates a reasonable fit of the regression model. The criticism is not that the model does not fit the data, but rather that the quality of fit means that caution should be used in interpreting the conclusions from the model. When the small scale of the cognitive benefits of propentofylline, as measured by the MMSE score, is taken into account, this caution should be redoubled.

Thus, in the light of these issues concerning the assumptions underlying the model, the fit of the model and the small differences in MMSE score being used with the model, there is grave concern that the cognitive benefits of propentofylline, which have little clinical relevance, would lead to delays in transition between care settings and the consequent cost reductions claimed.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

These are:

1. Not to purchase propentofylline and to review the situation in the light of further research evidence becoming available on this and other drugs for dementia.

2. To support the purchasing of propentofylline only within appropriate RCTs and other studies designed to answer specific questions in relation to the use of this drug.

3. To purchase propentofylline within an agreed protocol defining selection and discontinuation criteria for the drug for a defined group of patients.

4. To support open prescribing of propentofylline for all patients with mild to moderate dementia for whom it is judged appropriate by clinicians specialising in the mental health care of older adults.

5. For health authorities to recommend appropriate research into this class of drugs to answer the questions on cost and benefits outlined in this report.

5. DISCUSSION AND CONCLUSIONS

5.1 General

There is limited published evidence that propentofylline produces a very modest benefit in global and cognitive function in patients with mild to moderate AD or VaD. While the benefit from drug therapy is statistically significant, there are methodological concerns regarding the meta-analysis of the four trials. Furthermore, the modest benefit reported fails to achieve clinical relevance where clinically relevant differences have been defined.

It is recognised that the Phase III programme was initiated prior to the widespread availability of the ADAS-cog instrument. However, the lack of local experience with all of the assessment scales used, excepting the MMSE, means that it is difficult to interpret the clinical implications of the published results. In the Marcusson paper, where results have been interpreted in terms of the ADAS-cog scale, and in the trials reported in conference posters, the ADAS-cog results are similarly very modest and certainly less than accepted clinically relevant thresholds.

Propentofylline has a different pharmacological basis for use in dementia from the two existing drugs, donepezil and rivastigmine. The latter are both cholinesterase inhibitors which have predominantly central neurotransmitter-related effects with limited peripheral activity, hence minimising toxicity. Propentofylline is, however, a phosphodiesterase inhibitor (cf. theophylline and caffeine) and an adenose re-uptake inhibitor. The relative and absolute significance of these activities in dementia is not fully substantiated. The results from the eight week withdrawal study of propentofylline suggest that it has a functional rather than purely symptomatic effect.

Practical difficulties are foreseen in monitoring the effectiveness of propentofylline in clinical practice in patients with VaD. It is accepted that nearly all patients with AD show a progressive deterioration and that it is theoretically possible to monitor patients, once they have started treatment, to identify those whose rate of deterioration seems to be slowing, plateauing or showing an improvement. With patients with VaD, however, there is great variability in the course of the illness and there may be long periods of time during which the patient is stable. Therefore, it is only those patients who are showing a convincing improvement over a three month period that one can confidently classify as responders. If the improvement is going to be as little as one point on the MMSE scale, then the sensitivity

and reliability of this test in serial measurements is an important issue. Futhermore, these issues have important implications when considering the practicalities of defining protocols for use and withdrawal of drug therapy.

The clinical evidence for propentofylline comes from one fully published RCT, two meta-analyses, including three further unpublished RCTs, and a number of, as yet, unpublished conference presentations. Thus, there is substantial concern that much of the evidence for propentofylline arises from unpublished trials.

Furthermore, it should be noted that the benefits shown in the published trial (Marcusson, et al.[9]) are approximately twice the size of the benefits shown in the meta-analysis, see Table 4. This raises a question over the size and statistical significance of the benefits shown in the remaining unpublished trials, covering over 800 patients, which must certainly have been less than the already modest benefits shown in the meta-analysis and may well, from the figures available, have been neither statistically, still less clinically, significant. It is recognised that there may well be valid methodological reasons for these differences. Therefore, the importance of full publication of individual trial methodology and results is reiterated.

A linear regression model has been claimed to demonstrate that propentofylline is likely to lead to a reduction in the cost of providing care and support to the dementia population and that this reduction would offset the additional drug costs. There are important methodological criticisms of this modelling exercise, principally, in the assumption that very modest benefits in cognition and global function will lead to corresponding changes in the support costs. Whilst it is undoubtedly true that only relatively small changes in care requirements would be required to offset the drug costs, the modelling exercise does not constitute substantial evidence. In order to address the economic issues of using propentofylline, further research is required either to validate the assumptions within the model or directly to assess the cost and consequences of therapy in an economic analysis alongside a clinical trial.

5.2 Recommendations for Further Research

Further research is required to examine the costs and consequences of the use of propentofylline. In particular, research is needed to examine whether there is any reduction

in the use of hospital, nursing home or community care services. Intermediate evidence validating the assumptions within the economic modelling would also be useful.

The impact on the health and quality of life of carers should be examined further, possibly using validated measures, such as, the Care Givers Activity Scale.

Further work is required on the development of validated and reliable assessment scales for measuring the quality of life of patients with dementia.

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