WORKING GROUP ON ACUTE PURCHASING

A Review of the Use of Donepezil in the Treatment of Alzheimer's Disease

December 1997

GUIDANCE NOTE FOR PURCHASERS 97/09
Series Editor: Nick Payne

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authority 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, and includes non-clinically qualified scientists and lay members. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of appropriate evidence, 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 20 January 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

Since this Guidance Note went to the Trent Development and Evaluation Committee, one of the main randomised controlled trials has been published (Rogers S et al., Neurology 1998; 50: 136-45). Its results do not make any substantial changes to the conclusions set out here.

A REVIEW OF THE USE OF DONEPEZIL IN THE TREATMENT OF ALZHEIMER'S DISEASE

AUTHORS: Pitt FA, Chilcott J, Golightly P, Sykes J and Whittingham M. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1997. Guidance Note for Purchasers: 97/09.

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DECISION: The Committee recommended purchasing donepezil within appropriate controlled trials and in other studies with agreed protocols with defined selection of patients and defined discontinuation criteria for the drug.

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A REVIEW OF THE USE OF DONEPEZIL IN THE TREATMENT OF ALZHEIMER'S DISEASE

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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.

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 Institute:

- provides advice and support to NHS staff on undertaking Health Services Research (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 Akehurst 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 Purchasing Authorities Chief Executives (PACE) 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, The Scottish Health Purchasing Information Centre (SHPIC) and The University of Birmingham Department of Health and Epidemiology.

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

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EXECUTIVE SUMMARY

Donepezil is one of a new group of selective acetylcholinesterase inhibitors which has been newly licensed in the UK for use for people with mild and moderate Alzheimer's Disease. The drug is marketed as having an effect on the symptoms of the disease, but it has no effect on the underlying disease process. The cost of donepezil is approximately £1,000 per patient per year.

Alzheimer's Disease affects about 8% of the population over 65 years of age. It is estimated that the number of people with mild to moderate dementia in a population of 500,000 is approximately 2,400. Prevalence is expected to increase over time with the ageing of the population and anticipated increase in the number of people over 85 years of age.

So far, evidence of efficacy is based on three randomised controlled trials of which only one, the Phase II trial, is published in full. The two Phase III trials, which are currently published in abstract form, looked at two treatments (5mg and 10mg) against placebo. A variety of outcome measures were used which measured changes in cognitive function and severity of the disease. Secondary outcome measures examined activities of daily living and quality of life for patients and carers. The trials examined the effects of donepezil over 12 weeks and 24 weeks respectively. A placebo washout followed both Phase III trials which showed that all treatment arms returned to the same cognitive function as the placebo group after six weeks removal of the drug.

The results of the trials showed modest improvement in cognitive function which were considered significant in research terms. It is unclear how much that improvement is translated into improvement in clinical functioning and quality of life for patients and carers.

Changes in clinical condition were reported using measures of global impression of change. However, these changes were minimal and the reliability of the scales has not been established. Measures of the impact on quality of life have not been validated for this patient group. Further work is required to examine the impact on clinical function, activities of daily living, the impact on health and well-being of carers, and whether the drug can effect a delay in the need for hospital care.

The effect of the drug is to give a slight improvement in cognitive function compared with placebo, and then a continued decline, delayed by approximately 12 weeks, but otherwise at

the same rate as the placebo group. The overall impact is a delay of progression of the disease of about three months. When the prescription is stopped, the effect is not sustained and the patient returns to the same cognitive functioning as would be expected if the drug had not been prescribed in the first place.

There was a reported large variation in response in all arms of the trial and it has been reported that some patients on treatment benefited significantly more than the average score for their treatment arm. This raises the question about whether there is a group of patients with Alzheimer's Disease who could benefit significantly more than others. The full trial results are required before this can be examined further. This raises potential questions for further research to examine the selection of a group of patients which has potential for greater benefit.

The trials suffered from high discontinuation rates in all arms, but in particular, the treatment arms. This was due to mild gastro-intestinal and neurological effects caused by the cholinergic effects of the drug which were clearly dose-related. No serious adverse effects were reported.

Costs include the cost of the drug and the cost of a potential increase in demand for specialist assessment and diagnosis. It is not clear how long people should be prescribed donepezil, although, the data show that the delay in symptoms can only be sustained whilst people are receiving treatment. There is no evidence available to suggest savings in the NHS or other agencies. The lack of data on potential savings and the other uncertainties not answered in the available research means that any calculation of cost utility would need to be based on some extremely broad assumptions. It is recommended that further research and work is carried out in this area.

1. INTRODUCTION

1.1 Background

Alzheimer's Disease (AD) is the name given to a group of dementias, a case of which was first described by Alois Alzheimer in 1907. It is the most prevalent category of dementia, possibly accounting for approximately 70% of cases.

The condition is usually sporadic, but can be familial, and several relevant genetic loci have been elucidated. Macroscopically there is progressive ventricular dilatation and global cortical atrophy with marked thinning of the parahippocampal gyrus.

The final common pathway in all cases seems to be the deposition of beta-amyloid protein in the form of neuritic plaques in the hippocampus and areas of cerebral cortex. Possibly secondary to plaque formation, neurofibrillary tangles form intracellularly and correlate in numbers to disease severity.

Loss of cholinergic neurones occurs especially in the nucleus basalis of Meynert whose cells project to the hippocampus and cortex. Whilst other neurotransmitter systems are involved later, cholinergic deficits are prominent early in the disease.

1.2 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, 60% of these having mild to moderate disease.

The most recent compilation of prevalence data for dementia comes from the work of EURODEM,[1] 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.

By applying the prevalence rates for all dementia using the results of the EURODEM study to an average health authority with a population of 500,000, (see Table 1), there are

estimated to be approximately 5,725 cases of dementia. Assuming that AD is responsible for approximately 70% of dementia in older adults, we would expect about 4,000 cases, of which around 2,400 would have mild and moderate disease.

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

Age group	Population	Prevalence of Dementia Male	Female	Expected Dementia	Expected AD	Mild and Moderate AD
45-64	112,756	0.06%	0.06%	68	47	28
65-69	24,184	2.20%	1.10%	393	275	165
70-74	22,022	4.60%	3.90%	928	650	390
75-79	15,056	5.00%	6.70%	906	634	380
80-84	10,838	12.10%	13.50%	1,411	987	592
85+	8,079	21.50%	26.20%	2,020	1,414	849
Total 45+	192,935			5,725	4,008	2,405
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 average health authority, with about 560 of these being of the Alzheimer's type each year.

1.3 Standard Management of Alzheimer's Disease

Currently, the clinical management of AD is focused on accurate diagnosis and provision of appropriate services to patients and carers. Diagnostic criteria such as D.S.M. IV and NINCDS-ADRDA[2] do not allow the diagnosis of AD in the presence of other brain disease and systemic disorders that may account for the dementia. The process of diagnosis, therefore, requires a search for other disorders to exclude other causes of dementia.

Although the process of diagnosis may be initiated before there is any substantial need for support services, it is often the latter which triggers the former. The delay in diagnosis may be due to the patients' lack of awareness of problems, a perception by patients and carers that forgetfulness is an untreatable part of ageing, or insufficiently sensitive screening in primary care and elsewhere.

When a patient has been identified as potentially suffering from dementia, possibly AD, the diagnostic process usually begins, normally in a primary care setting. Referral to secondary care tends to occur when specialist services are required or in cases of diagnostic difficulty.

The essential elements of diagnosis are:

1. A full medical history corroborated by a close relative or carer;
2. Mental state examination including cognitive assessment;
3. Physical examination;
4. Routine screening blood and urine investigations; and
5. Special investigations.

1.4 Treatments for Alzheimer's Disease

Donepezil hydrochloride ("Aricept") is a distinct new piperide-based cholinesterase inhibitor. It is a reversible and specific inhibitor of acetylcholinesterase. Its characteristic is that it minimises peripheral cholinergic effects which cause side-effects in other agents. The long plasma half-life (up to 70 hours) not only permits once-daily dosing but also produces a gradual approach to steady state.

Donepezil is only the first of a number of drugs likely to reach the UK market in the next two or three years. Over 150 drugs in development have been identified, of which over 70 are in Phase II or Phase III trials or in a pre-registration phase. These drugs have a wide variety of pharmacological actions. Whilst it is acknowledged that many will not reach the market for safety, efficacy or commercial reasons, many are likely to be successful. It is predicted that up to 10 drugs could be available in the UK within the next five years.

The initial focus on new drugs for AD has been on cholinesterase inhibitors. When drugs from other pharmacological groups are introduced, there will be the potential for tailoring treatment to individuals' clinical requirements and symptoms, and for the development of combination therapy, using two or three drugs to cover a spectrum of symptom control. Early clinical trials of combination therapy are currently being considered in the USA.
Drugs currently under clinical development, with marketing potential in the next two to three years in the UK are summarised in the Appendix. There are currently no significant clinical trials known to be underway directly comparing drugs for Alzheimer's with each other.

There is no evidence to suggest that other cholinesterase inhibitors will have any different effects or activity compared to donepezil. Eventually, differences between drugs in terms of symptom specificity or adverse effects may be shown. Differences may depend on the degree of reversibility of the cholinesterase inhibitor effects, but this is currently only speculation.

It is expected that rivastigmine ("Exelon") will be marketed in the UK in early 1998, followed by propentofylline in mid to late 1998. Other drugs may follow in late 1998 or 1999.

Propentofylline will probably have an additional indication for vascular dementia, whilst sabeluzole is being evaluated for its ability to slow the progression of the disease rather than as a palliative treatment for the symptoms.

2. USE OF DONEPEZIL : SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Available Evidence

There have been three randomised controlled trials (RCT) of donepezil in the USA of which only one has been published in full: the Phase II trial[3] involving 161 subjects on 1mg, 3mg and 5mg doses. Recently, the results from the two pivotal Phase III trials (A301 and A302)[4] have been completed. The first trial has been published in abstract form,[5] so full details of the study methods have not been published at the time of writing this report. Patients were from a highly selected group, exclusion criteria including: patients without a reliable caregiver, insulin dependent or having unstable diabetes, having evidence of other psychiatric or neurological disorders, or patients with dementia complicated by other organic disease.

Both Phase III trials were multi-centre, randomised, double-blind, placebo-controlled, three armed trials comparing patients on 5mg and 10mg of donepezil with a single-blind placebo washout at the end of the trial period. The first trial (468 patients) looked at outcome over 12 weeks with a three week washout period. The second trial (473 patients) looked at treatment over 24 weeks with a six week washout phase.

The Phase II trial was followed by a cohort study (A202) where patients in the trial were offered 7mg or 10mg after the placebo washout and were studied for up to two years. 133 patients were enrolled in this study and only 42 completed the trial at 98 weeks. There was no control group. This provides the longest follow-up data for donepezil but the trial is unpublished.

There is a European multicentre study, involving around 750 patients, which has been completed, but for which the data are not yet available.

2.2 Outcome Measures Used

Primary Outcome Variables

1. *The Alzheimer's Disease Assessment Scale*[6] - 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-retest

reliability, it has been described as 'too sensitive to change'[7] 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; the deterioration is not linear, there being marked variation between individuals depending on initial severity.

2. A revised version of the *Clinician Interview Based Impression*[7] (*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-retest reliability of CIBIC plus is poor, although reliability is a problem for all subjective measurements.

Secondary Outcome Variables

1. The *Mini Mental State Examination (MMSE).*[8] This 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. Levels of 10 to 26 correspond to mild to moderate dementia.

2. *Activities of Daily Living* (*ADL*). The ADL is designed to examine the patient's management of every-day living skills including selecting and preparing food, dressing, eating, hygiene, mobility, orientation, communication, housework and managing finances.

3. *Clinical Dementia Rating-Sum of the Boxes* (*CDR-SB*). This is a measure of disease severity in dementia and has a maximum possible score of 18. The scale shows good reliability and is derived from semi-structured interviews with the patients and primary caregiver in six categories (memory, judgement, orientation, problem solving, community affairs, home and hobbies and personal care).

4. *Quality of Life scores as assessed by the patient or caregiver* (*QL-P and QL-C*). These are generic measures in the following categories: working, leisure, eating, sleeping,

social contact, earning, parenting, loving, environment and self-acceptance. Some of these variables are less applicable to patients with AD. This scale has not been validated for use with patients with dementia and their carers.

2.3 Review of Trial Results

Table 2 below identifies the currently available studies of donepezil and summarises their main characteristics. It should be noted that the only trial to have been fully published at the time of writing this report and, consequently, to have passed through the refereering process for publication, is the 12 week Phase II trial. The evidence upon which this drug has been licensed has not yet been published in full and is only available in abstract form.

Furthermore, the Phase II trial which has been published only included dosages of 1, 3 and 5mg in the treatment arms. Therefore, there is to date no complete, refereed information available on the 10mg dosage which is licensed and being marketed alongside the 5mg dosage.

Table 2 Summary of Studies of Donepezil[9]

NAME OF STUDY	STUDY DESIGN	DOSE	NO. OF SUBJECTS	DURATION	STATUS
Rogers et al [3]	Phase II RCT	1,3,5 mg	161	12 weeks' treatment 2 weeks' washout	Published
A301	Phase III RCT	5,10 mg	468	12 weeks' treatment 3 weeks' washout	Unpublished
A302	Phase III RCT	5,10 mg	473	24 weeks' treatment 6 weeks' washout	Published
A202	Cohort extension study to Phase II trial	1,3,5-7,10mg NB no control group	133		Unpublished
European multicentre study			750		Unpublished

Cognitive Function

The RCTs showed statistically significant differences between treatment and placebo groups in the ADAS-cog scores. All patients, including control patients, initially showed

some improvement in the ADAS-cog score which may have been due to the placebo effect or a learning effect in the early weeks of the trial.

Figure 1 details the patient response in terms of ADAS-cog score over the 30 weeks (24 weeks treatment, six weeks placebo washout) of Phase III trial, A302. Patients were given a baseline ADAS-cog assessment at randomisation, followed by further reassessments at six weekly intervals up to 30 weeks. Figure 1 presents the mean change from baseline scores for each of the three treatment arms. The treatment effect is defined as the difference between the mean change from baseline for the treatment group and the mean change from baseline for the placebo group.

In this 24 week trial, the mean treatment effect at 24 weeks was -2.52 points on the 70 point ADAS-cog scale for the 5mg group and -2.87 for the 10mg group (p=0.0007 for 5mg and 0.0001 for 10mg). Pair-wise comparison of effect between the two treatment arms was not available, although the reported differences would not be detectable clinically.

In the 12 week trial, A301 (12 weeks treatment, 3 weeks placebo washout), the mean treatment effect at 12 weeks was -2.48 points on the 70 point ADAS-cog scale for the 5mg group and -3.12 for the 10mg group (p<0.0001).

Table 3 Changes in ADAS-cog in Phase III (12 week and 24 week) Trials

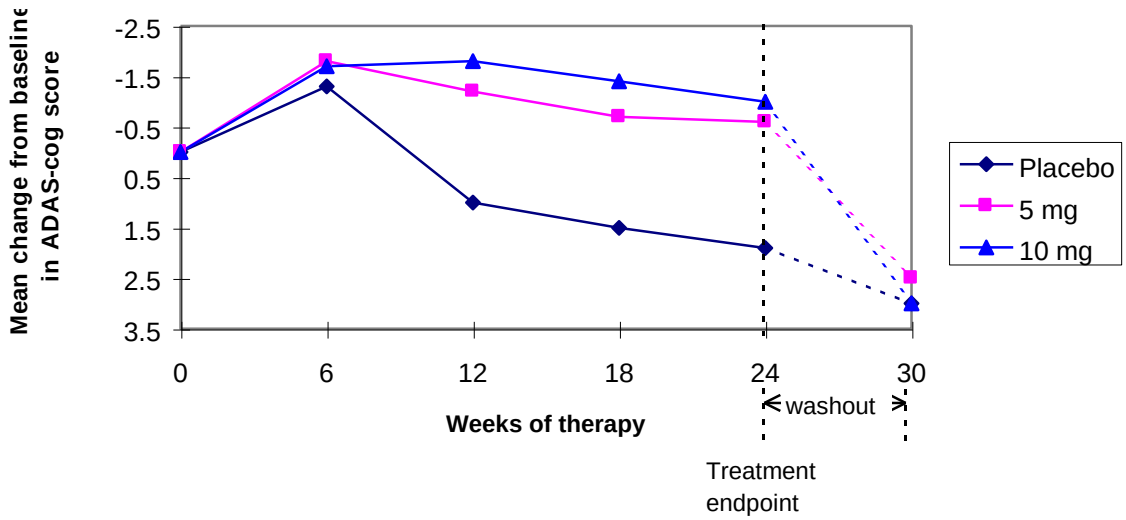
	5mg	**10mg**
A301 Treatment effect at 12 weeks (endpoint)	-2.48	-3.12
p value		p<0.0001
A302 Treatment effect at 24 weeks (endpoint)	-2.52	-2.87
p value	p=0.0007	p=0.0001

After withdrawal of treatment, cognitive status declined in all patients in all the trials. In the 24 week study no significant differences in ADAS score from baseline were maintained in either of the treatment arms after all patients were given six weeks of placebo.[5]

A major problem with the Phase III trials is that only summary data have been made available. A considerable variation of response between patients in all the arms of the trials has been reported. This needs to be looked at in detail when the full results are made available. The reported range of change in the ADAS-cog score is from +10 (worsening) to

-15 in all groups. Over 80% in both treatment groups showed some response over baseline compared to 60% in the placebo group. 26% of the 10mg group showed an improvement of over seven points on the ADAS-cog compared to 15% of the 5mg group and 8% of the placebo group. There is anecdotal evidence that a few patients in the treatment arms showed considerable clinical improvement. However, there were no data to show which group of patients could benefit the most, or if this heterogeneity of response was significantly different from the placebo group.

Figure 1 Effect on Cognitive Function over 24 Weeks as Measured by the ADAS-Cog[10] From Trial A302.



Functional Status

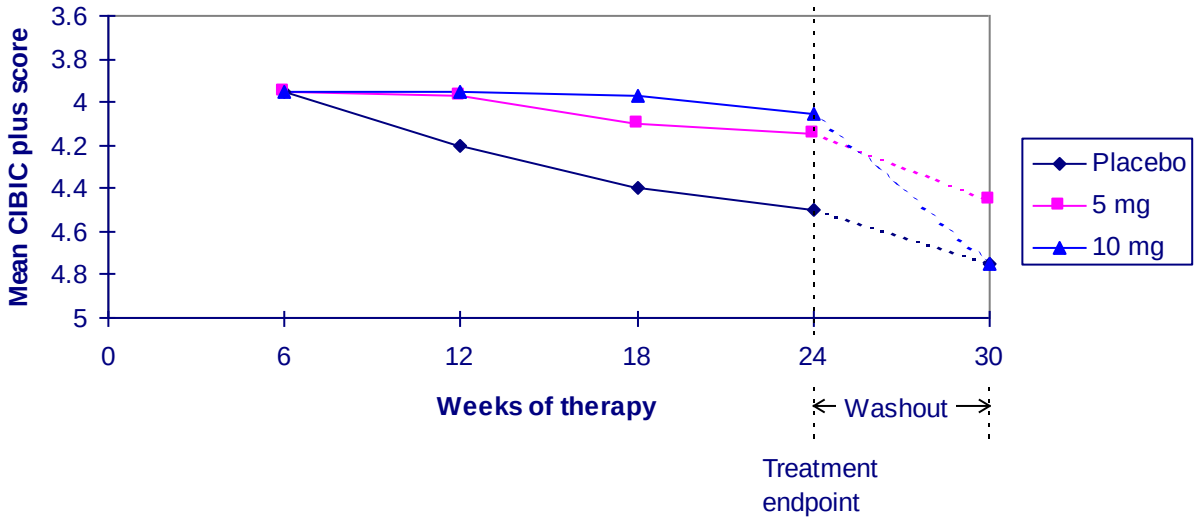
Clinical change in condition was assessed using the CIBIC plus scale. Table 4 shows the mean scores at endpoint for the various arms of the Phase III 12 week trial. At trial endpoint approximately twice as many donepezil treated patients demonstrated some improvement compared to placebo. That improvement resulted in a small statistically significant effect for donepezil over placebo, that is a difference of 0.29 points on the CIBIC plus scale, from a mean score of 4.19 for placebo group to 3.9 in the 5mg/day group in the 12 week Phase III trial A301.

Table 4 Results of CIBIC Plus Scoring in the 12 Week Phase III Trial A301

Placebo	5mg/day	10mg/day

CIBIC plus score at 12 weeks	4.19	3.9	3.85
p value		0.0026	0.0082
Proportion of patients showing some improvement	18%	32%	38%

Figure 2 - Effect on Global Function over 24 Weeks as Measured by CIBIC Plus.[10]



Severity of Disease

In the 24 week Phase III trial, A302, a positive result is reported for the CDR-SB scores. The placebo group worsened compared to some small improvements over baseline for both treatment groups.

Table 5 Changes in the CDR-SB Score in 24 Week Phase III Trial A302

Placebo	5mg	10mg
0.58	-0.03	-0.02

Longer-term data are available from the cohort study. The CDR-SB scores improved during the 12 week treatment of the RCT phase, followed by a stable period slightly worse than at baseline, and then gradual worsening. This is difficult to interpret in the absence of a control group or data on normal disease progression, as measured using the CDR-SB scale.

Quality of Life

A positive dose response was shown in the Phase II trial, although pairwise comparisons between groups showed no significant response. The quality of life scales used in all the RCTs have not been validated for this group of patients and some of the variables in the scale have little clinical relevance to this patient group. Further research is called for in this area perhaps using other measures including a full assessment of the impact on the caregiver.

Activities of Daily Living

No significant effects have been reported in the information currently available.

Side Effects and Adverse Events

Donepezil has not been shown to have any serious side-effects over the reported lengths of the trials.[5] The main effects are cholinergic symptoms which include: headache; gastrointestinal symptoms; muscle cramps; insomnia; dizziness and fatigue. There are patient groups in which special precautions should be taken because of the cholinergic nature of the drug. There is a lack of evidence about concomitant use of other drugs, in particular psychotropic drugs, which may also be used in this patient group.

The trials reported a high discontinuation rate, in particular in the treatment arms, which may be due to the cholinergic side-effects (Table 6) which appear to be dose-related. One factor may be the inability in a trial situation to titrate dosage according to response and production of cholinergic side-effects which may be managed better in a clinical situation.

Theoretical warnings about the use of donepezil because of its cholinergic effects include the use of anaesthesia, history of peptic ulcer, sick sinus syndrome, bladder obstruction, epilepsy or history of fits and history of chronic obstructive airways disease.

Table 6 Comparison of Adverse Events and Numbers Discontinued in the Three Arms of the Phase III Trials

A301 - 12 week trial

	Placebo	**5mg**	**10mg**	**Total**
Study population	153	157	158	468
Completed study	93%	90%	82%	88%
Discontinued	8%	11%	22%	14%
Serious adverse events	9%	0%	7%	5%

A302 - 24 week trial

	Placebo	**5mg**	**10mg**	**Total**
Study population	162	154	157	473
Completed study	80%	85%	68%	78%
Discontinued	25%	18%	48%	29%
Adverse events	34%	39%	47%	42%

3. COSTS AND BENEFITS

3.1 Summary of Potential Costs and Benefits of Donepezil

Benefits	**Disbenefits**
1. Improved cognitive function for patients with mild or moderate AD - equivalent to approximately a 12 week delay in symptom progression. 2. Improved functional status for patient - modest improvement in CIBIC plus score. 3. Improved quality of life for patient - no clear evidence. 4. Improved quality of life for carers - no objective evidence available. 5. Reduced morbidity in carers - no objective evidence available.	1. Side-effects from treatment See Section 3.3.
Savings	**Costs**
1. Possible savings made in the NHS (e.g. by delayed hospital entry) - no evidence available. 2. Possible savings in reduced need for nursing/residential home care - no quantitative evidence available. 3. Savings made in other areas of society (e.g. reduction in benefits, reduction in home care required) - no quantitative evidence available. 4. Increased earnings by patient or carers. - no quantitative evidence available.	1. Cost of the drug £891 per annum @ 5mg per day £1,248 per annum @ 10mg per day 2. Possible cost due to side-effects (hospitalisation, non-hospitalisation) - no evidence available. 3. Increased cost of diagnosis and assessment.

3.2 Benefits

Cognitive Function

The most reliable effects of donepezil appear to be on cognition as measured by the ADAS-cog and MMSE. Measured improvement in cognitive status was shown in the first three to six months of treatment. The evidence from the studies suggests an improvement in cognition and a delay in cognitive decline of approximately three months.

Functional Ability

There is no significant evidence to suggest that donepezil improves functional status. Benefits as measured on the CIBIC plus are difficult to interpret. Although having good face-validity, the scale is not standardised and has poor test-retest reliability. As the memory test components of the CIBIC carry most weight, it is not clear whether the positive effects reflected the cognitive benefits as measured on the ADAS-cog. The benefits were small and may, therefore, be of less clinical significance.

Similarly, the results of the effects using the CDR-SB score, although more relevant to clinical status than the ADAS-cog, were small compared to placebo and cannot easily be taken into account in an analysis of the benefits of donepezil.

The early plateau in CDR-SB in the cohort study suggests some delayed progression, although without controls this is difficult to interpret. Further results may be available on full reporting of the Phase III 24 week study, A302, to allow comparison with controls. At present the available published results have not shown definitively any improvement in functional ability using reliable methods.

Quality of Life for Patients and Carers

The results show no significant evidence as yet of improvement in quality of life either for patients or carers.

3.3 Disbenefits

Side-effects experienced in the trials showed significant minor neurological and gastrointestinal side-effects as shown in the table below. A lower rate of adverse effects was reported when the dose was titrated from 5mg to 10mg over six weeks.

Table 7 Summary of Side-Effects Across all Trials.

	Treatment	Placebo
Gastrointestinal symptoms (diarrhoea, nausea, vomiting)	31%	22%
Neurological symptoms (headache, insomnia, dizziness, syncope)	32%	25%

Although several patients in the cohort study experienced syncope or falls, this is difficult to interpret without a control group. While a decrease in blood pressure was also noted in the 24 week Phase III trial, A302, the mean change of -3.45 mmHg was not considered significant.

3.4 Costs

Cost of Donepezil

The costs per individual per year of donepezil treatment are:

5mg = £891 per annum based on 28 tablets @£68.32
10mg = £1,248 per annum based on 28 tablets @£95.76

There is a lack of evidence about the best point to stop treatment.
Estimating the likely duration of treatment, and therefore costs, is difficult. The most widely quoted estimates of survival for patients with AD are between five and eight years. However, this may be longer with earlier diagnosis and better treatment and care.

Cost of Early Referral

It has been hypothesised that the advent of a specific treatment for patients with mild to moderate AD would encourage early referral and assessment. It has been recommended that this drug should be initiated by clinicians specialising in the mental health of older adults after clinical assessment. Whether this would be included as an additional cost burden depends on how memory clinics function.

There is evidence[11] to suggest that, even without cognitive enhancing drugs, there is benefit to patients and their carers of early assessment and diagnosis to allow early preparation and adjustment to the effects of the disease, to ensure the introduction of support services at the appropriate time and to exclude treatable causes of dementia.

3.5 Savings

There is no direct evidence to suggest that any savings could be made by reduction of the treatment costs, reduction of hospital treatment or hospitalised care.

Improvement in practical self-care skills or in support required by carers was not measured.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

1. Not to purchase the use of donepezil.

2. Not to purchase the use of donepezil and to review the situation in the light of research evidence becoming available on this and other drugs for dementia (see Appendix).

3. To purchase the use of donepezil within appropriate RCTs and other studies designed to answer specific questions in relation to use of this drug.

4. To press for appropriate research into this class of drugs to answer the questions on costs and benefits outlined in this report.

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

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

5. DISCUSSION AND CONCLUSION

There is clear evidence that donepezil is efficacious in producing some improvement of cognitive functioning in a highly selected population with mild to moderate AD, although much of the evidence is as yet unpublished, except in abstract form. The evidence shows that it will delay the progression of the disease by approximately three months, though whether this is of real clinical significance is uncertain. There is no evidence, as yet, to show that donepezil has any effect on disease end-point or on the overall rate of decline in the long-term.

No significant improvement in activities of daily living, or on quality of life were shown using the measures in the studies reviewed. Further research could usefully be caried out on quality of life and the impact on primary carers, using measures such as the Care Givers Activity Scale (CGAS).

More data and analysis are required on the variations in clinical response between patients. Considerable variety in response was found such that small numbers of patients improved much more than average on the ADAS-cog scale. It may be that there is a group of patients who may benefit from this drug more than other patients. However, it is not possible to predict from the available trial data which patients could benefit the most, which would allow informed treatment protocols to be written, or whether this variation in disease progression is significantly different from the variation which occurred in the placebo group.

There is no definite evidence for significant efficacy of the 5mg dose compared with 10mg, although the side-effects are clearly dose-dependent. The drug, however, is licensed for both 5mg and 10mg use.

It was not possible to make any meaningful analysis in terms of costs and consequences given the dearth of evidence on many aspects of the cost and benefits and a large number of assumptions which would have to be made in order to assess these.

This review illustrates once again the problems associated with the introduction of new drugs on the basis of limited published data on efficacy and before the results of definitive trials are published. Donepezil has potentially large cost implications for the NHS because of the large number of eligible patients. Research questions are raised on the evidence that is available about the clinical efficacy of the drug, as applied to the population of people with

AD, and its cost-effectiveness compared to other priorities for this patient group and other new technologies in general. This raises questions about the criteria on which drugs receive a licence in the UK, including whether these should include sufficient research on efficacy and proof of cost-effectiveness.

Recent reviews[9,12] of the evidence which have been published have reached very similar views about the effectiveness of donepezil and raised similar questions about gaps in knowledge, which would need to be researched in order to make a definitive statement about the cost-effectiveness of this drug and the relative priority it should assume for health service expenditure.

5.1 Recommendations for Further Research

1. Further work is required to examine the cost and consequences of the use of donepezil. In particular, research is needed to examine whether there is any reduction in use of hospitals, nursing homes or community care associated with its use.

2. 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.

3. More data are required about the heterogeneity of response of patients on treatment compared with those on placebo, to examine whether there is a particular group of patients who could most benefit from use of the drug and how these patients could be identified.

4. The long-term effects of the drug should be compared with placebo, including an examination of whether efficacy is maintained and for how long.

5. Patients entering the trials were from a highly select group and may not be typical of the average patient with AD in the UK. The effect of the treatment in the average clinical situation, as against a trial setting, should be explored.

6. USE OF DONEPEZIL IN THE TREATMENT OF MILD AND MODERATE ALZHEIMER'S DISEASE : SUMMARY MATRIX

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Patients with mild and moderate dementia of Alzheimer's type.	To be agreed, preferably on the basis of future research showing evidence of clinical effectiveness for particular groups of patients.	Approximately 2,400 adults over 45 years of age in a HA with a population of 500,000. Potential cost of drug could be between £2.1 million and £3.0 million (excluding assessment costs) if all eligible patients received treatment.	Unlikely, as no evidence of reduced hospital or nursing home costs.	Slight improvement in cognition. Possible slight improvement in function. Delay in disease progression 3 to 6 months.	Largely unproven.

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APPENDIX - New Drugs for Alzheimer's Disease Currently under Development and with Marketing Potential in 1997- 1999

Drug name	Manufacturer	Pharmacological class	Development status	Earliest marketing	Clinical summary
Galantamine	Shire	Cholinesterase inhibitor	Launched in some countries. Phase III Europe	1998/99	**Therapeutic Trials:** Two clinical trials, an open pilot study in 19 patients and a double-blind, placebo-controlled crossover study in 79 patients with Alzheimer's disease (AD), used the Cognitive Drug Research (CDR) system, to evaluate changes in patients' cognitive function during treatment with galantamine or tacrine. The double-blind study consisted of two 12-week treatment periods with placebo or tacrine separated by a 4-week washout period. 32 patients underwent CDR testing. In both trials, the CDR system provided evidence of improvement in cognitive function during active treatment [1]. In a separate study, 106 patients with mild to moderately severe AD were treated with galantamine (20-50mg/day PO) [*duration of treatment not stated*]. Significant improvements were seen on the Alzheimer's Disease Assessment Scale (ADAS), Mini-Mental State Examination (MMSE) and Physicians Global Evaluation scales[2] 167 patients with mild to moderate AD took part in a multicentre dechallenge trial. All patients received placebo for a 1-week run-in period, and then received galantamine 20 mg/day for 3 weeks. After titration to determine the best individual dosage (50mg/day), the 112 pateints who had not had a significant placebo response or drug intolerance, but did have a significant response to galantamine were randomised to either continue with galantamine (56) or receive placebo (56) for a double-blind 10-week maintenance/dechallenge phase. The 141 patients who completed the 3-week single-blind galantamine phase had a dose-related improvement in the ADAS cognitive subscale of 5.14 points. Responders randomised to continue with galantamine improved by a further 1.66 points, while those switched to placebo deteriorated by 1.4 points [3]. In another study of a similar size, patients were randomised to therapy with galantamine 22.5, 30 or 45mg/day given tid or placebo for 10 weeks. Preliminary data obtained from 163 patients indicated that patients receiving the 2 highest doses of galantamine had better cognitive ADAS scores relative to placebo (> 5 point difference) [3]. In a 3-year open follow-up study, intermediate data for 19 patients at 24 months and 11 patients at 36 months indicated that patients receiving galantamine 10-35 mg/day ± other treatments such as nootropics or antidepressants continued to show a significant benefit compared with patients who did not receive galantamine or any other acetylcholinesterase inhibitors. However, the stabilisation of ADAS cognitive score observed at 12 months had begun to wear off at 24 months [3]. The final results of a 3-month phase II study involving 285 patients demonstrated a mean improvement in ADAS cognitive score of 4.3 points in patients receiving

Drug name	Manufacturer	Pharmacological class	Development status	Earliest marketing	Clinical summary
					galantamine 30 mg/day relative to placebo recipients (p = 0.001). The preliminary results of a 6-month phase III trial including 550 patients investigating the efficacy of galantamine 40 mg/day tid indicated highly significant improvements in cognition, as measured by the cognitive ADAS score, as well as in secondary efficacy measures, including a clinical global rating and an activities of daily living scale [4] **Adverse Events:** Agitation, Arrhythmias, Bradycardia, Diarrhoea, Dizziness, Hypersalivation, Sleep disorders, Nausea, Vomiting
Metriphonate	Bayer	Cholinesterase inhibitor	Phase III (Europe/ USA)	1998/99	**Therapeutic Trials:** High dose metrifonate improved Alzheimer's Disease Assessment Scale (ADAS) and Mini-Mental State Examination (MMSE) scores in a double-blind study involving 27 patients with Alzheimer's disease. The compound was safe and well tolerated [5]. In a multicentre randomised double-blind phase II trial in patients with probable Alzheimer's disease, medium and higher doses of metrifonate had significant effects on the ADAS-Cognitive and Clinicial Interview Based Impression of Change-Plus primary outcomes compared with placebo (FDC Reports Pink Sheet 1996 Aug 19). **Adverse Events:** Agitation, Constipation, Diarrhoea, Gastrointestinal disorders, Malaise, Nausea, Paraesthesia, Vomiting, Cardiovascular disorders
Milameline	Hoechst Marion Roussel and Warner-Lambert	Muscarinic receptor agonist	Phase III trials in Europe and USA	1999/ 2000	**Therapeutic Trials**: A double-blind study in 10 elderly patients (aged 59-74 years) with Alzheimer's disease (NINCDS criteria) evaluated the safety and tolerance of multiple rising oral doses of milameline. Doses of milameline ranged from 0.5-3mg and were administered q6h over 19 days. The study was terminated following the fourth 3mg dose because of concerns over safety. Trough plasma levels of milameline were proportional to daily dose over the range 2-10mg/day. In the light of these results, the maximally tolerated dose of milameline was 4-8mg/day [6]. **Adverse Events:** Diaphoresis, Hypersalivation, Nausea, Chills, Diarrhoea, Headache, Sweating
Nefiracetam	Daiichi Seiyaku	GABA receptor agonists	Pre-registration (Japan)		**Therapeutic Trials:** In a dose-finding study, a 450 mg/day dosage of nefiracetam was significantly more effective than a dosage of 150 mg/day among 289 evaluable patients with cerebrovascular disorders (81% with cerebral infarction). Patients received either of these regimens, or a 300 mg/day dosage, for 8 weeks in a double-blind trial. Final global improvement ratings of 'moderately improved or greater' were documented in 24.5%, 28.4% and 41.7% of patients receiving, respectively, the 150, 300 and 450 mg/day dosages. Psychiatric symptoms responded best: these were 'moderately improved or greater' in 32% of patients given the dosage of 450 mg/day [7]. Mean total scores for the Hasegawa Dementia Rating Scale (HADRS), which

Drug name	Manufacturer	Pharmacological class	Development status	Earliest marketing	Clinical summary
					measures cognitive function, increased significantly overall in patients receiving long term nefiracetam therapy (up to 1 year) in 2 studies with similar protocols [8,9]. Nefiracetam 150mg tid (titrated to a maximum of 900 mg/day) for at least 8 weeks [8] or 6 months [9] was given to patients who had predominantly psychiatric symptoms, usually following cerebral infarction. The change in HADRS was significant in patients with baseline scores >10 and £30. HADRS scores worsened in 12.9% of patients in 1 study [9]. Symptom improvement according to final global rating scores in these studies was 'moderate or greater' in 42% [8] and 46.2% [9] of patients. Improvement was gradual and most benefit was gained within 6 months. Nefiracetam treatment was rated 'moderately useful or greater' in 43.6% [8] and 44.6% [9] of patients. It was rated 'undesirable' in 3.1% of 65 patients [9]. Improvements were greatest in psychiatric symptoms ('moderately improved or greater' in 47.4% [9] and 34% [8] of patients) and were least noticeable in activities of daily living [8,9]. Nefiracetam 150mg tid for 8 weeks was superior to placebo as measured by percentage of patients with a final global improvement rating of `moderate or greater' (32.3 *vs* 10.1%, p < 0.001), global usefulness ('useful' in 32.1 *vs* 10.9%, p < 0.001), and overall improvements in psychiatric symptoms ('moderate or greater' in 30.8 *vs* 10.9%, p < 0.001). There were significant between-group differences favouring nefiracetam in the individual symptoms of apathy, emotional disturbance, interpersonal contact and general cognitive dysfunction [10]. A multicentre double-blind trial in 258 patients compared nefiracetam 150mg with idebenone 30mg, each given 3 times daily for 3 weeks. Patients in the nefiracetam group manifested more severe psychiatric symptoms at baseline. Nefiracetam treatment was rated 'useful' in 39.7% of patients, significantly more than with idebenone (26.9%, p < 0.05). Nefiracetam also tended to show greater efficacy as assessed by the final global improvement rating and overall improvement rating for psychiatric symptoms: for both scales 37.6% of patients given nefiracetam versus 26.9% of idebenone recipients were judged 'moderately improved or greater' using intention-to-treat analysis. Improvement ratings for individual psychiatric symptoms and most other measures tended to be higher with nefiracetam but not significantly so. Mental function, including memory, improved in more patients treated with nefiracetam than with idebenone (p < 0.05) [11]. **Adverse Events:** Dizziness, Rash, Gastrointestinal disorders, Anorexia, Blepharoedema, Nausea, Sweating, Tinnitus
Propentofylline	Hoechst Marion Roussel	Adenosine uptake inhibitors	Pre-registartion (Europe)	mid 1998	***Propentofylline will be addionally indicated for vascular dementia*** **Therapeutic Trials:** The long-term efficacy of propentofylline in patients with dementia has been investigated in a multicentre, randomised, placebo-controlled, double-blind study. Patients with DSM-III-R criteria for mild to moderate dementia of the Alzheimer's

Drug name	Manufacturer	Pharmacological class	Development status	Earliest marketing	Clinical summary
		Phosphodiesterase inhibitor	Phase III (USA) Launched elsewhere		(n = 170) or vascular (90) type were randomised to receive propentofylline (n = 129) 900 mg/day tid for 12 months or placebo (131). At 12 months, the total patient population exhibited significant treatment differences in favour of propentofylline for the global measures of dementia, including the Gottfries-Bråne-Steene scale ($p = 0.001$), and the Clinical Global Impression scale item I ($p < 0.01$) and item II ($0.1 < p < 0.05$). Cognitive measures also revealed treatment differences in favour of propentofylline, including the Syndrome Short Test ($p < 0.01$) and the Mini-Mental State Examination ($p = 0.001$). Activities of Daily Living, as assessed by relatives and nursing staff, deteriorated in both patient groups, but less so in propentofylline recipients ($p < 0.01$). Treatment differences for the primary efficacy variables were smaller for patients with Alzheimer's disease than patients with vascular dementia, but all were in favour of propentofylline[12]. 2 further trials are currently awaiting publication from which there is no prior information.
Rivastigmine	Novartis	Cholinesterase inhibitor	Pre-registration (Europe, USA)	early 1998	**Therapeutic Trials:** Preliminary data from a phase III 26-week study involving 699 patients with Alzheimer's disease showed that rivastigmin was well tolerated and associated with significant improvements in all efficacy/cognitive function measures, including the ADAS cog and CIBIC-Plus. In a phase II dose-finding study, patients with mild to moderate Alzheimer's disease were assigned to 1 of 3 treatment groups (2 fixed doses of rivastigmin or placebo) for 13 weeks. Each group contained > 100 patients. A significant proportion of patients treated with rivastigmin showed a positive response on the Clinical Global Impression of Change scale. Smaller improvements were noted on 2 other scales. In what appears to be a separate dose-finding study, 50 patients received rivastigmin 2-12 mg/day or placebo for 9 weeks. Although no maximum tolerated dose was defined, the compound was generally well tolerated up to dosages of 12 mg/day [13]. Data presented at the 16th World Congress of Neurology indicate that rivastigmine improved cognition, global functioning and activities of daily living in patients with Alzheimer's Disease. These findings were from a 6-month follow-up of 2,096 patients with symptomatic mild to moderately severe Alzheimer's Disease. Patients were randomised to receive either high dose (6-12 mg/day) or low dose (1-4mg/day) treatment with rivastigmine or placebo. The cognitive scale of the Alzheimer's Disease Assessment Scale (ADAS-cog) decreased by 4.15 points in placebo recipients, but improved by 0.79 points in rivastigmine recipients. The difference in scores translated into a clinically relevant delay in deterioration of about 6 months. According to the Clinician's Interview-Based Impression of Change, placebo recipients deteriorated by 0.48 points, while high-dose rivastigmine recipients deteriorated by 0.13 points and low-dose recipients deteriorated by 0.16 points. The between-group differences in

Drug name	Manufacturer	Pharmacological class	Development status	Earliest marketing	Clinical summary
					scores were significant. Scores on the caregiver-rated Progressive Deterioration Scale were significantly better in high-dose rivastigmine recipients than placebo recipients. It is becoming apparent that the benefits of rivastigmine are greatest in patients with more severe disease [14]. **Adverse Events:** Diaphoresis, Dizziness, Headache, Nausea, Vomiting
Sabeluzole	Janssen	Calcium channel antagonists	Phase II UK Phase III Belgium, USA	1998/99	***Sabeluzole is being evaluated for its ability to slow the progression of the disease rather than as a palliative treatment for the symptoms*** **Therapeutic Trials:** In a double-blind placebo-controlled study, 53 patients with age-associated memory impairment were treated with sabeluzole 20 mg/day or placebo for 2 months. Although no significant between-group differences were detected during the study period, sabeluzole recipients had significant improvement over baseline in Word Fluency Test (WFT) scores as well as in the quality of memory function. 62% of sabeluzole recipients *vs* 49% of placebo recipients felt that their memory had improved [15]. A long-term follow-up of 34 of these patients at the end of 10 months of open treatment with sabeluzole found that performance in the cued recall task and WFT significantly improved over the long term. In contrast with the results of the short-term study, improvement was also seen in the selective reminding procedure. Of 23 patients evaluated for memory function by their physician, none worsened, 5 were unchanged, 11 had mild improvement, 4 had moderate improvement and 3 had marked improvement. Over the 1-year duration of the study these patients would have been expected to significantly deteriorate [16]. Treatment with sabeluzole, 10 or 20 mg/day (bid) for 1 year, was compared with placebo in patients with probable Alzheimer's disease. 33 patients, ranging from 53 to 79 years of age, underwent computerised tomographic (CT) scans. 17 patients were rescanned after treatment. Although sabeluzole treatment was associated with a reduction in the rate of deterioration, an analysis of CT scans revealed no statistically significant structural correlates [17]. In a study involving 48 patients from 1 centre participating in a multicentre study of 401 patients, 48 weeks' treatment with sabeluzole was not associated with any significant difference in mean group scores for the Clinical Global Impressions scale compared with placebo. According to Alzheimer's Disease Assessment Scale scores, the placebo group deteriorated to a significantly greater degree than the sabeluzole group [18]. In a study involving 38 patients with partial epilepsy and memory impairment, sabeluzole was associated with significant improvements on the verbal long-term memory tests. This was thought to be potentially beneficial for epileptic patients who often display subjective complaints representing deficiencies in the retrieval of verbal

Drug name	Manufacturer	Pharmacological class	Development status	Earliest marketing	Clinical summary
					information[19]. **Adverse Events:** Headache, muscle/joint pain, irritability, dizziness, weight gain, nausea and difficulty breathing, all of mild severity, have been reported during treatment with sabeluzole.
Tacrine	Parke Davis	Cholinesterase inhibitor	Product licence UK.	Marketed in USA, but unlikely in UK	**Therapeutic Trials:** Oral tacrine, in dosages of 80 to 160 mg/day, has been shown to improve cognitive function and behavioural deficits in a proportion of patients with Alzheimer's disease in 2 double-blind placebo-controlled parallel design trials of 12 and 30 weeks' duration. A significant dose-response relationship was demonstrated at dosages of up to 160 mg/day. Between 40 and 58% of patients entering the studies were withdrawn during treatment for various reasons (mainly adverse events). However, of the evaluable patients in these trials, 30 to 51% achieved an improvement on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-C) of at least 4 points, compared with about 16 to 25% of those receiving placebo. The difference in ADAS-C scores between placebo and tacrine 80 and 160mg recipients remained statistically significant with intention-to-treat/last observation carried forward analyses. Clinician-rated global outcome measures were judged to have improved in 25 to 42% of evaluable patients receiving tacrine 80 to 160 mg/day for 30 weeks, compared with 15 to 18% of placebo recipients. These results were substantiated by a third parallel design trial using a dose-titration phase, and by the results of some tests in 6 crossover design trials, although several of these studies have been criticised for such aspects as the possible development of training and carry-over effects, low dosages, low patient numbers, and administration of confounding concomitant medication. Nonetheless, responding patients were observed in most trials [20]. A trial involving 460 patients with Alzheimer's disease showed that patients without the Apolipoprotein E4 allele improved more with tacrine treatment than those with the allele [21]. The combination of tacrine and lecithin produced no treatment advantage over tacrine alone in a double-blind, crossover study involving 440 patients with Alzheimer's disease [22]. Tacrine also showed potential for the treatment of dementia in patients with Parkinson's disease. In the 7-patient study, the frequency of hallucinations was greatly reduced in all patients following tacrine treatment; they were eliminated in 5 patients. All patients displayed improvements according to Folstein Mini-Mental State scores and Unified Parkinson's Disability Rating Scale scores. Improvements in gait roughly corresponded to improvements in mentation [23]. **Adverse Events:** Anorexia, Ataxia, Dyspepsia, Hallucinations, Liver disorders, Rash, Rhinitis, Seizures, Vertigo, Diarrhoea, Elevated aminotransferase levels, Nausea,

Drug name	Manufacturer	Pharmacological class	Development status	Earliest marketing	Clinical summary
					Vomiting
Xanomeline	Eli Lilly	Muscarinic M1 & M4 receptor agonist	Phase III USA	1998/99	*The pattern of adverse events, particularly gastrointestinal, associated with the oral formulation of xanomeline, has prompted the development of a transdermal xanomeline formulation,* **Therapeutic Trials:** The effects of xanomeline on cognition, behaviour and global status have been assessed in a double-blind, placebo-controlled trial in patients with mild to moderate Alzheimer's disease. 343 patients were randomised to therapy with xanomeline 75 mg/day, 150 mg/day or 225 mg/day, or placebo, tid for 6 months. A completer analysis of the cognitive subscale of the Alzheimer's Disease Assessment Scale disclosed a significant treatment effect with xanomeline 225 mg/day ($p < 0.05$ *vs* placebo). Completer analysis of the clinician's global assessment, measured by the Clinician's Interview-Based Impression of Change, disclosed a significant drug effect with xanomeline 150 and 225 mg/day ($p < 0.05$). Treatment emergent signs and symptoms analysis of the Alzheimer's Disease Symptomatology Scale indicated that xanomeline dose-dependently, and at the 225 mg/day dose, significantly reduced vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, mood swings and threatening behaviour. Xanomeline dose-dependently prevented the onset of these symptoms in patients in whom they were absent at baseline. End-point analysis of the Nurses' Observational Scale for Geriatric Patients revealed a significant dose-dependent improvement in activities of daily living, social behaviour and disturbing behaviour; memory, self-care and mood were not significantly affected on this scale [24]. **Adverse Events:** Chest pain, Chills, Dyspepsia, Dysphagia, Faecal incontinence, Salivary gland disorders, Syncope, Diarrhoea, Nausea, Sweating, Vomiting

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