

Drug treatment of dementia

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The second part of our special feature deals with the treatment options available for the various forms of dementia

Currently, most patients with dementia are managed in the community. However, with the advent of disease-modifying therapy, hospital specialists (usually in psychiatry, especially old-age psychiatry, neurology or medicine for the elderly) are increasingly involved in diagnosis and management of the condition.

Pharmacists in both secondary and primary care may contribute to the

pharmaceutical care of individual patients. The introduction of drugs for use in mild-to-moderate Alzheimer's disease, for example, means that there is an increasing need for health care professionals to work with patients earlier in the disease. Many of these patients are on long term medication, thus requiring comprehensive advice and support.¹

The establishment of memory clinics and development of services for people with dementia also provides an opportunity for primary and secondary care pharmacists to make another contribution to the care of these patients. This may be through individual pharmaceutical care, contributing to the development and implementation of guidelines, and liaising at the primary/secondary care interface. Pharmacists providing these services need to work in partnership with other health care and social services professionals, as well as the person with dementia and the family carer. In addition, underdetection of dementia is recognised as a

significant problem and may contribute to the risk of medication errors.^{1,2} Pharmacists may have a role in identifying problems with medication in this patient group.

It is essential that patients with apparent cognitive impairment are fully assessed to ensure as accurate a diagnosis as possible and to identify and treat any reversible causes of cognitive impairment, such as depression or hypothyroidism.

Drug treatments can be divided into four categories:

1. Cognitive enhancement
2. Treatment of behavioural and psychological aspects
3. Possible disease modifying agents
4. Potentially harmful agents

COGNITIVE ENHANCEMENT

There are several theoretical approaches to the development of agents for the treatment of dementia. Currently, the most

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important of these is the cholinergic hypothesis.

Cholinergic hypothesis of AD Systematic biochemical studies of the brains of patients with Alzheimer's disease were conducted in the late 1960s and early 1970s in an attempt to establish a clearly defined neurochemical abnormality, which would allow development of specific pharmacological interventions. This was supported by studies in the middle to late 1970s and early 1980s which concluded that a substantial presynaptic cholinergic deficit exists in Alzheimer's disease. This occurs through a variety of mechanisms including deficits in choline acetyltransferase, which is the enzyme responsible for the synthesis of acetylcholine (ACh), reduced choline uptake and reduced ACh release.⁴

The original "cholinergic hypothesis of Alzheimer's disease" was developed from these studies together with a knowledge of the emerging role of ACh in learning and memory. The hypothesis proposed that degeneration of cholinergic neurones and associated loss of cholinergic neurotransmission contributed significantly to the cognitive decline seen in Alzheimer's disease.⁵

In almost 20 years since it was originally published, numerous studies have challenged the cholinergic hypothesis. A recent review proposed a glutaminergic hypothesis as an auxiliary to the cholinergic hypothesis.⁴ This states that a major target of cholinomimetic action is excitatory amino acid (EAA) pyramidal neurones, and that reduction in cholinergic functioning compounds the loss of EAA activity. Thus, although the hypothesis has been refined, the role of cholinesterase inhibitors is actually further strengthened by these new proposals which confirm the importance of the cholinergic system in Alzheimer's disease.⁴

Cholinesterase inhibitors Various strategies to boost the cholinergic system in Alzheimer's disease have been proposed. Initial trials of ACh precursors, such as lecithin and choline, proved ineffective as they do not increase central cholinergic activity. Unacceptable adverse effects have precluded development of postsynaptic cholinergic receptor agonists.⁶

Research has therefore focused on cholinesterase inhibitors where results have been encouraging. These agents act by increasing cholinergic transmission in the synaptic cleft by reducing the hydrolysis of ACh released from presynaptic neurones. The cholinesterase inhibitors differ in their chemical class, relative reversibility, and selectivity for different cholinesterases.⁷

Currently, only donepezil, rivastigmine and galantamine are marketed in the UK. They are licensed for the symptomatic treatment of mild to moderately severe dementia

Panel 1: Costs associated with dementia care²⁶

Direct costs

Hospital care
Medical care (both primary and secondary care)
Nursing home care
Respite care
Medications

Indirect costs

Time lost from activities
Premature loss of life
Informal caregiving by family and friends (may include lost opportunities for paid employment)

Possible impact of drugs on care costs

Delay in institutionalisation or increased length of time living at home, resulting in increased or decreased quality of life for patient and increased or decreased quality of life for caregiver
Adverse effects: additional costs associated with adverse effects (and monitoring for these)
Diagnostic difficulties: implications for patient selection where there is currently limited evidence of efficacy in non-AD dementias

of the Alzheimer's type. Last month, the National Institute for Clinical Excellence (NICE) issued guidance that these three drugs should be made available to specified patients in England and Wales.⁸

Donepezil and rivastigmine are, respectively, reversible and pseudoirreversible inhibitors of cholinesterase, while galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, in addition to its activity as a reversible cholinesterase inhibitor.⁹

Tacrine was approved in the UK at the same time as donepezil, but was not marketed. Its usefulness was limited by potentially serious hepatotoxicity.¹⁰

Although, at present, these agents are only licensed for mild-to-moderate Alzheimer's disease, there is emerging evidence that they may be at least as useful in patients with other forms of dementia.^{11,12}

There are reduced choline acetyltransferase levels in dementia with Lewy bodies (DLB), thus greater benefit may be expected with the agents^{13,14} and preliminary data have shown improvement in behavioural symptoms.¹⁵

There have also been a few case reports indicating possible benefits of cholinesterase inhibitors in patients who have severe dementia.¹⁶

Trial data In 1997, the Committee for Proprietary Medicinal Products (CPMP) produced guidelines that efficacy of drugs for dementia should be demonstrated in two areas – cognitive function and either a global rating or activities of daily living (ADL) scale.¹⁷ Published trials of donepezil, rivastigmine and galantamine show that efficacy over placebo is clearly established for each drug in terms of cognitive improvement.^{10,18} Details of published trials are available in the NICE guidance.⁸

In large group studies, there has been a definite clinical improvement (eg, 4 to 5 points on the ADAS-COG scale which measures cognitive function) in 40 to 50 per cent of patients and improvements have also been seen using cruder measures such as MMSE (mini-mental state examination) over three months. There is also some evidence of improvement in non-cognitive symptoms of psychosis and apathy.^{15,19,20}

Clinical effectiveness A consensus as to the place of these expensive agents in clinical practice has yet to be reached.²¹ Differences in the approaches to the prescription of cholinesterase inhibitors by various health authorities, boards and trusts have been highlighted in a recent survey.²² Various mechanisms have been used to manage the introduction of these new drugs into practice.^{23,24} Part of the difficulty in reaching agreement as to the effectiveness of these drugs lies with problems in interpretation of the published evidence. Clinical response in individual patients may be difficult to predict from changes in rating scale scores presented in clinical trial papers.²¹ An alternative method of interpreting such data, which aims to make randomised controlled trial (RCT) information more useful for clinical decision making, is the concept of "number needed to treat" (NNT).²⁵ This concept, which is widely accepted by advocates of evidence based medicine, conveys both statistical and clinical information intelligibly. The NNT is "the number of patients who need to be treated with the treatment in question, compared to another treatment (often placebo) for one patient to gain a specified benefit".

An NNT analysis of selected RCTs for tacrine, donepezil and rivastigmine²¹ showed very small NNTs of mostly between 3 and 7 when cholinesterase inhibitors were used at appropriate doses. The outcomes related to postponement or reversal in deterioration. Higher doses were associated with smaller NNTs. The small NNTs suggest an important place in the current clinical management of Alzheimer's disease, but health economic data are also required.

Pharmacoeconomics Pharmacoeconomic arguments relate to the currently huge direct and indirect costs of managing patients with Alzheimer's disease. Panel 1

Panel 2 : Counselling points with cholinesterase inhibitors

Expectations of patient or carer and limitations of treatment
End-point of treatment (should be negotiated at beginning of treatment)
Compliance issues
Side effects and what to do about them
Carer role in compliance and monitoring for adverse effects
Consent for treatment
Use of rating scales in assessing patient's progress

highlights some of the direct and indirect costs associated with dementia care and some potential impacts of drugs on the cost of patient care.

Use of cholinesterase inhibitors may allow patients to stay at home longer and hence shift the burden of care to the family and primary care team. However, it is unclear whether this results in a reduction of overall costs, and effect on life expectancy and quality of life also need to be considered.²⁶ Most of the economic studies carried out in this area are limited by issues such as diagnostic difficulties and the undefined clinical benefit of the drug, as most data are from clinical trials of short duration. It is difficult to assign values to unpaid caregiving which probably represents a high percentage of the costs.²⁷ There may be less interest in these informal costs than formal costs such as nursing home placement. Conclusions from the substantial number of published studies range from cost-saving to expensive but further work is needed.^{27,28,29}

Other issues contributing to the pharmacoeconomic debate on AD include shifting patterns of institutional care, due to policy changes in many countries, and the increased potential for strategies such as respite care and sheltered housing.³⁰

Some of the practical aspects to be considered in initiating treatment with cholinesterase inhibitors include:

- Identification of potential responders
- Eligibility for treatment initiation
- Choice of cognitive enhancer and prescribing issues
- Assessment of response and whether to continue treatment

Panel 2 lists some of the aspects of treatment that should be discussed with the patient.

Identification of potential responders The suggestion that the presence of apo-E $\epsilon 4$ allele (see first part of special feature) may help identify potential responders to cholinesterase inhibitors has not been con-

firmed, and should not be used to guide treatment.

There is some emerging evidence on the use of positron emission tomography to measure acetylcholine neurotransmission binding, with the potential to monitor altered cholinergic function during the clinical course of the disease and help identify potential responders to treatment.³¹

Eligibility for treatment initiation The September, 2000, edition of the British National Formulary recommends that treatment with cholinesterase inhibitors should be initiated and supervised by a specialist experienced in the management of dementia.³² This recommendation is derived from a Standing Medical Advisory Committee guideline.³³ The availability of a family carer to ensure compliance is important.

The type and severity of dementia is important in guiding treatment, and it raises various issues. The cholinesterase inhibitors are only licensed for the treatment of mild to moderate Alzheimer's disease, but emerging evidence suggests that they may also be effective (and perhaps even more so) in DLB. Although local treatment protocols may only allow use of the treatments in AD, there is often a mixed picture of more than one type of dementia, which may influence prescribing practice.

Limitations in the assessment scales used should also be considered when making decisions about starting or stopping treatment. For example, patients with AD who have a high pre-morbid intelligence quotient (IQ) may score greater than 26 on the MMSE scale and people with speech and language difficulties may score less than 10, but this should not necessarily exclude either group from treatment.

Patients who have severe dementia, or mild cognitive impairment (which may develop into dementia) are not in general currently considered eligible for treatment, although further research is ongoing.

Various cautions and contraindications should be considered, including asthma, seizure disorders, chronic obstructive airways disease, epilepsy, bladder outflow obstruction, history of peptic ulceration or significant bradycardia.

Choice of cognitive enhancer There is no clear evidence to suggest that one agent is more effective than another and side effect profiles are similar. Frequency of dosing, side effects and co-existing morbidity may be relevant in the individual patient. For patients who live alone, once daily dosing is often preferred and so donepezil may be the drug of choice.

Side effects are usually cholinergic in nature and are generally mild to moderate, of short duration and usually resolve spontaneously or on dose reduction. Some side effects are shown in Panel 3. These can be

Panel 3 : Side effects of cholinesterase inhibitors

Fatigue
Nausea and vomiting
Dizziness
Diarrhoea
Headache
Syncope
Other cardiovascular effects
Anorexia and weight loss
Agitation and confusion
Dyspepsia
Increased sweating
Tremor

NB: Rivastigmine, galantamine and donepezil are currently "black triangle" drugs, ie, pharmacists should report all suspected side effects to the Committee on Safety of Medicines using the yellow card scheme

minimised by starting at a low dose and increasing gradually according to response and tolerability, as shown in the Table.³⁴ Some local protocols recommend trying another cholinesterase inhibitor if the drug is not tolerated, but not to do so if there is lack of response.

Assessment and continued treatment Current guidelines for treatment tend to use symptomatic effect as a marker for showing the benefit of an AD drug, but the next stage may be to slow disease progression and additional biological end-points may be required to assess this in future, for example, using neuroimaging techniques.³⁴ Desired end-points of treatment may include decreased carer burden and stress, increased time until long term care is required, stabilisation of memory or cognition, and decline in various symptom domains.

The mainstay of assessment is cognitive assessment which should be repeated after around three months treatment. This may give a guide to response, though it is impossible to predict how the disease would have progressed in the absence of treatment. Up to half of patients may show a slower rate of cognitive decline than would be expected if untreated. It is recommended that the agent be discontinued in those patients who do not appear to be responding.

In practice, many specialists repeat the cognitive assessment four to six weeks after discontinuation of treatment and consideration may be given to restarting the drug if significant deterioration occurs within this timescale. Experience with these drugs indicates that approximately 60 to 70 per cent of patients may continue these drugs long term.

There is some evidence to suggest that an initial three month assessment may be insuf-

Table: Dose titration of cholinesterase inhibitors

Drug	Starting dose	Dose titration	Maximum dose	Available strengths	Cost for 28 days (MIMS, Nov 2000)
Donepezil	5mg once a day at bedtime	Reviewed after one month, increased to 10mg daily if well tolerated	10mg daily (some local protocols keep dose at 5mg)	5mg, 10mg	5mg per day (£68.32) 10mg per day (£95.76)
Rivastigmine	1.5mg twice daily	Increased in steps of 1.5mg twice daily at minimum fortnightly intervals	6mg twice daily	1.5mg, 3mg, 4.5mg, 6mg	6mg twice daily (£63.00)
Galantamine	4mg twice daily for four weeks	After four weeks, initial maintenance dose is 8mg twice daily, for at least four weeks, then consider increase to maintenance dose of 12mg twice daily	12mg twice daily	4mg, 8mg, 12mg	8mg twice daily (£68.32) 12mg twice daily (£84.00)

NB: Slower titration of doses is often used in clinical practice. For example, rivastigmine may be increased at monthly, rather than fortnightly intervals. This may require delaying the decision about continuing treatment as it may take longer to reach a therapeutic effect.

ficient, and some centres continue treatment for an additional 12 weeks in patients who are not yet showing clear clinical benefit but where the drug is well tolerated.³⁵

Assessment of outcomes other than cognitive function, including the carer's assessment of overall functional benefit, may also be useful. There is no evidence on when to stop these drugs after long term use and this issue needs to be addressed.³⁶ It is important that this is discussed with the patient and carer at the start of treatment with cholinesterase inhibitors. Some factors that may be considered include:

- Poor compliance (highlights importance of liaison with carer)
- Poor tolerance or side effects, including behavioural disturbance
- Additional psychiatric or physical illness, especially severe respiratory, cardiovascular or gastrointestinal illness
- No evidence of benefit
- Entry to long term care (due to disease progression)

Future of cognitive enhancement

Agents such as lecithin and choline, which are acetylcholine precursors, have shown no evidence of efficacy.^{37,38}

New cholinesterase inhibitors are being developed. Metrifonate showed some initial promising results in trials, but the request for approval in Europe was withdrawn following reports of muscle weakness.³⁹

Other cholinesterase inhibitors currently being studied include slow release physostigmine, eptastigmine, zifosilone and quilostigmine.

Melamiline and xanomeline are cholinergic muscarinic agonists under trial⁹ as is the precursor loading agent, acetyl-L-carnitine.^{9,40} The effect of cholinesterase inhibitors on disease progression is not clear, but in the future there is likely to be more interest in drugs which may potentially slow the progression of the disease. This will be discussed below).

BEHAVIOURAL TREATMENT

Non-cognitive behavioural changes, such as depression, aggressive behaviour, psychosis and overactivity, often start between two and eight years after the start of cognitive symptoms, usually in conjunction with marked cognitive decline, and they generally increase with severity of dementia. These symptoms are difficult to manage, are a common cause of caregiver stress and a major reason for admission to long term care.⁴¹ There is some evidence to suggest an association with cholinergic disturbance, and a possible role for cholinomimetics requires further research.⁴²

The management of these aspects of dementia has been reviewed by the Scottish Intercollegiate Guidelines Network (SIGN) and the North England Evidence-Based Guidelines in Primary Care Management of Dementia project, which give similar recommendations.^{43,44}

Consent to treatment is a particularly relevant and difficult issue in the treatment of behavioural disturbances. Difficulties may arise in terms of carers, health care staff and relatives giving medicines without consent.⁴³ People with dementia may retain some mea-

sure of insight and so should be involved in decisions regarding their own care.⁴⁵ The added aspect of unlicensed use of some of the drugs adds to the difficult issue of consent.

Informed consent is also an important aspect of cognitive enhancement and requires sharing of the diagnosis with the patient and family. Caregivers' perception of the acceptable risk-benefit ratio of medication may be influenced by various factors. For example, caregivers who are working, adult children caring for early stage patients, and families with a history of dementia may tolerate higher risk.⁴⁶ As dementia progresses beyond the mild stage, patients may lose insight into their condition and so may decline treatment.

New legislation in Scotland, Adults with incapacity (Scotland) Act, 2000, reforms the law in this area and provides a framework for decisions on treatment. Similar legislation is being considered for England and Wales.

Non-drug interventions, either instead of or in addition to drug treatments, should be considered, and used judiciously, particularly in mild behavioural disturbance. These include reality orientation, behavioural intervention, occupational activities, environmental modification, validation therapy, reminiscence and sensory stimulation.

Drug treatment A number of pharmacological agents are considered below.

Trazodone Although there is little published supporting evidence, trazodone is well established in clinical practice in the UK and is often used first line where pharmacologi-

cal treatment is indicated for behavioural problems, avoiding the side effects associated with antipsychotics. It is useful for symptoms of agitation and aggression, although is only specifically licensed for depression.

Conventional antipsychotic drugs Antipsychotic drugs have been widely used, but the evidence for their efficacy is limited. They are generally overused, particularly in hospitals and nursing homes,^{47,48} where non-drug approaches may be more appropriate, and antipsychotic drug withdrawal may be possible in some patients.⁴⁹ The anticholinergic effects of these drugs contribute to confusion and progression of cognitive impairment. They should not be given to patients where DLB is suspected (see below).

There is some evidence of improvement in behavioural problems, but this is limited by lack of standard assessment measures, variability in patient populations studied, and short trial durations and there is a high placebo response rate.⁵⁰ Potentially irreversible long term side effects such as akathisia and tardive dyskinesia may be common in this patient group. The drugs should be restricted to use in patients with serious problems, in particular psychotic symptoms, or in the presence of serious distress or danger from behaviour disturbance. There is no clear evidence to guide choice of one drug over another, but extrapyramidal and anticholinergic side effect profiles should be considered.

Thioridazine has been widely used, often inappropriately, in this patient group. Recent concerns about QT prolongation have resulted in restriction of its product licence to second line treatment of schizophrenia only. Various local guidelines for managing this change are being developed at the time of writing. A reasonable approach would be slowly to withdraw the drug from elderly patients being treated for behavioural problems. An alternative antipsychotic need not automatically be substituted, and withdrawal reactions or rebound agitation are uncommon. However, in severe cases, low doses of

Panel 4 : Minimising adverse effects of neuroleptics

- “Start low, go slow”, that is, use low doses initially, with slow and cautious increase as necessary
- Keep treatment short term and review regularly
- Reduce the dose as soon as possible and stop treatment if no longer essential
- Avoid neuroleptics where there is a possibility of DLB
- Side effects, such as akathisia or tardive dyskinesia, may be irreversible. Balance these against any perceived benefits
- Distinguish between akathisia, which is a common side effect of these drugs (characterised by subjective sensation of restlessness and a decreased ability to sit still) from worsening agitation, to avoid inappropriate dose increases and enable the drug to be stopped or the dose lowered
- Routine use of anticholinergic medication to prevent extrapyramidal side effects is not appropriate

an alternative antipsychotic, such as haloperidol 0.5 to 1mg, may be required. Panel 4 outlines some of the precautions to take if an antipsychotic is deemed necessary.

Atypical antipsychotics Atypical antipsychotics such as risperidone, olanzapine and quetiapine have been researched with some favourable results, compared with placebo or haloperidol, but the data are limited, and consist mainly of short term uncontrolled trials, case reports and retrospective chart reviews.

The drugs appear to be well tolerated, with a low incidence of extrapyramidal or anticholinergic side effects, including a lower incidence of tardive dyskinesia in elderly patients compared with conventional

antipsychotics. They are also effective in treating behavioural symptoms of dementia when used at low doses.⁵¹⁻⁵⁴

Much of the available data relate to risperidone, although this use is unlicensed at present. It may be particularly useful for treating acute agitation in patients at high risk of extrapyramidal side effects and for long term treatment of “sundowning” — when behavioural disturbances occur or become worse during the evening or night, but improve or disappear during the day.

Other agents There is limited evidence of benefit with gabapentin for treatment of aggressive and agitated behaviour in patients with dementia.⁵⁵ It may be considered in patients who have not responded to, or are intolerant of, neuroleptics. There do not appear to have been any published studies on its use specifically in DLB, where neuroleptics are generally contraindicated, and other agents would be considered before gabapentin in this patient group.

A small retrospective study indicated that valproate may have more benefit than lorazepam for treatment of agitation or anxiety related to dementia in long term care but further work is needed to confirm this.⁵⁶

Panel 5 shows other agents with limited evidence of efficacy in managing the behavioural aspects of dementia. Side effects must be considered carefully. For example, any possible benefits of benzodiazepines need to be balanced against their contribution to confusion and falls and hence these agents should usually be avoided.⁵⁷

Antipsychotics and DLB The danger of administering antipsychotics to patients with DLB has been well documented.^{18,58} These patients are at high risk of neuroleptic sensitivity, including neuroleptic malignant syndrome, associated with significant morbidity and mortality. This occurs even at low doses and with newer antipsychotics.⁵⁹ Antipsychotics should therefore be avoided if features suggestive of DLB are present, and used only with extreme caution where absolutely necessary. The behavioural prob-

Advertisement

Panel 5: Other drugs used in behavioural treatment*

Lithium
Beta blockers
Anxiolytics
Selegiline
Anticonvulsants (eg, carbamazepine, valproate, gabapentin)
Anxiolytics and hypnotics (eg, diazepam, nitrazepam, oxazepam, chlormethiazole and buspirone)
Trazodone
SSRIs including citalopram⁷⁰
Anticholinesterase drugs

*There is currently insufficient evidence of benefit of any of these drugs to make recommendations on their use in the management of behavioural and psychological aspects of dementia⁴³

lems associated with this type of dementia may be particularly difficult to manage. Some authorities suggest trazodone or cholinesterase inhibitors may be considered in this form of dementia, although they are not licensed for this specific indication.

Antidepressants Antidepressants can be used in the short term for marked and persistent depression, which often responds well.^{43,60} The only substantial data relate to moclobemide, although this is not generally considered first line therapy. Trazodone or a selective serotonin re-uptake inhibitor (SSRI) may be useful, started at low doses (eg, half the usual adult dose). Co-morbidity, interacting drugs and side effect profiles should guide treatment choice and strongly anticholinergic agents such as amitriptyline should be avoided.

Hypnotics or anxiolytics Hypnotics or anxiolytics may be used short term for severe and persistent symptoms of insomnia or anxiety.⁴³ These symptoms may be features of dementia. The SIGN guidelines highlighted the need to follow the British National Formulary guidelines on prescribing these agents.³² Long-acting preparations should be avoided in the elderly.

POTENTIAL DISEASE-MODIFIERS

No currently available agents have been shown to modify the course of dementia. There has been a great deal of interest in the protective effect of various agents already available for other indications, such as oestrogens and non-steroidal anti-inflammatory drugs (NSAIDs), but the evidence for this is controversial and largely based on retrospective and epidemiological studies.⁶¹ These agents are unlicensed for this indication and there is insufficient information

regarding risk and benefit to recommend them at present.

There is some evidence that primary and secondary prophylaxis of cerebrovascular disease may influence vascular dementia.

In the absence of any "cure" for dementia, patients and their relatives may turn to alternative medicine, including herbal remedies. The implications of administering an unlicensed agent and the issue of consent and liability for any mishap needs to be considered when discussing these issues with patients and their carers. Many of these agents are advertised and freely available from outlets such as health food stores, and also via the internet.

Oestrogens There has been much interest in the neuroprotective role of oestrogen in Alzheimer's disease, particularly in its potential use in helping symptoms early in the disease.⁶² There is some preliminary evidence to suggest that postmenopausal oestrogen may reduce the risk and delay the onset and progression of Alzheimer's disease.⁶³ However further work is needed to confirm this.⁶⁴⁻⁶⁶

In patients who already have Alzheimer's disease, oestrogen replacement therapy has not shown improvements in disease progression, or reduced cognitive, global or functional impairment.⁶⁷⁻⁶⁹

NSAIDs and COX-II inhibitors Several epidemiological studies and a small pilot clinical trial have reported a protective effect of prolonged anti-inflammatory use against Alzheimer's disease.⁷¹ This may not extend to other types of dementia.⁷² The clinical evidence available is conflicting and has been criticised for methodological bias. Various mechanisms for a neuroprotective effect have been suggested.

There is support for the hypothesis of a direct contribution of the inflammatory response to the neurodegeneration in Alzheimer's disease, consistent with the findings of immune and inflammatory markers in senile plaques. This suggests that long term anti-inflammatory drug treatment might delay the onset of the disease or at least slow disease progression.

The recent development of cyclo-oxygenase (COX)-II inhibitors (rofecoxib, celecoxib) with the possibility of better tolerance in the elderly is of interest, but further work is required.⁷³ Prospective randomised controlled trials of NSAIDs and COX-II inhibitors are currently being undertaken.

Selegiline and antioxidants Selegiline and alpha-tocopheryl, given in combination, have demonstrated some delay in progression of Alzheimer's disease.⁷⁴ A small study of selegiline given alone showed no benefit in cognitive or behavioural assessments.⁷⁵ Both agents have antioxidant properties as well as selegiline's effects as a

monoamine oxidase B inhibitor.⁷⁶ Selegiline is not currently recommended for this indication and any potential benefits may be outweighed by side effects, which include psychotic symptoms, particularly in DLB, and postural hypotension.⁷⁷

The American Psychiatric Association guidelines suggest that it would be reasonable to consider prescribing vitamin E at normal doses (200 to 800 IU per day) on the basis of some limited evidence of benefit,⁷⁸ the low potential for toxicity at these doses, and the lack of interaction with other agents. However, this is not routinely prescribed in the UK.⁷⁹ There have also been concerns over a higher incidence of falls in patients treated with vitamin E.

There is no good evidence for efficacy of other antioxidants such as idebenone.

Herbal medicines Numerous Oriental and European plant-derived compounds have been suggested with no evidence of benefit⁸⁰ or safety. Some plant-derived alkaloids may have the property of being able to inhibit acetylcholinesterase, which could theoretically result in drug interactions with prescribed medicines.

There has been an enormous amount of interest in the use of *Ginkgo biloba* for preventing and treating dementia but there is no conclusive evidence of benefit. The slight improvement in cognitive symptoms suggested by some sources is insufficient to recommend its use.⁸¹⁻⁸⁶

Many of the trials have been carried out in poorly defined populations with small sample sizes and using non-standard outcome measures, and the risk of adverse effects is unknown.

Vascular dementia Vascular dementia is currently thought to be the only potentially preventable form of dementia, by primary and secondary prevention of cerebrovascular disease. However, it is not known whether the use of evidence-based prophylaxis of cerebrovascular disease will lead to a corresponding reduction in this type of dementia, partly due to the difficulty with defining and diagnosing this type of dementia, and the heterogeneity of patients recruited into trials.⁸⁷⁻⁸⁹ In practice, known risk factors for ischaemia should be sought and addressed where possible.

Hypertension, for example, is a risk factor for cognitive impairment and dementia, and there is some evidence to suggest that appropriate antihypertensive treatments, including calcium channel blockers, may reduce not only stroke and cardiovascular complications, but also the incidence of dementia, including Alzheimer's disease.^{90,91} This needs to be studied further.

Aspirin is widely prescribed in patients with vascular dementia and up to 80 per cent of patients with cognitive impairment in the presence of vascular risk factors may

be prescribed aspirin.⁹² The benefit on cognition or prognosis is unknown, as is the question of whether this benefit outweighs risk of cerebral or gastric haemorrhage.⁹³

Statins Lipid-related mechanisms may contribute to the pathogenesis of dementia and there is epidemiological evidence to suggest that statins may lower the risk of developing dementia in patients aged 50 years or over, independent of the presence or absence of untreated hyperlipidaemia, or exposure to other lipid-lowering agents.⁹⁴ The implications of this for future treatment strategies is still unclear and further research is still going on.

Future for disease-modifiers There is a great deal of current research into understanding the pathogenesis and developing treatments for dementia. Four categories of pathogenic events may guide targets for treatment:⁹⁵

1. Primary events: genetic factors, neuronal apoptosis
2. Secondary events: beta amyloid deposition in senile plaques and brain vessels, neurofibrillary tangles due to hyperphosphorylation of tau proteins and synaptic loss
3. Tertiary events: neurotransmitter deficits, neurotrophic alterations, neuroimmune dysfunction and neuro-inflammatory reactions
4. Quaternary events: excitotoxic reactions, free radical formation, primary and/or reactive cerebrovascular dysfunction

As well as the further work being carried out into agents such as oestrogens and NSAIDs, particular interest is being shown in possible development of a number of agents, for example:

- vaccines against the beta-amyloid proteins found in plaques
- modulation of neurotransmitter systems other than the cholinergic system, for example glutamergic transmission
- use of NMDA (N-methyl-D-aspartate) antagonists as neuroprotective agents based on age-related change in NMDA receptors

— POTENTIALLY HARMFUL AGENTS

Certain agents should be avoided where possible in patients with dementia or pre-existing cognitive impairment.^{96,97} Drugs implicated include:

- Anticholinergics, eg, antidepressants, oxybutynin, thioridazine
- Long-acting benzodiazepines, eg, diazepam, nitrazepam
- Other psychoactive drugs, eg, barbiturates, dopaminergic drugs, opioid analgesics
- H₂ receptor antagonists, especially cimetidine

Many other drugs can cause confusion, often as a symptom of toxicity. This is more common in elderly patients where renal or hepatic metabolism is impaired. These include digoxin, long acting hypoglycaemics, anticonvulsants and NSAIDs. They

need not be avoided in people with dementia, but should be used with caution and appropriate monitoring. Various other problems may co-exist in patients with dementia, particularly given the demographics of this patient population. The usual difficulties with compliance and consent may arise. Pharmacists should be vigilant for medication which may either exacerbate dementia or interact with drugs prescribed to treat the dementia. Polypharmacy may contribute to confusion and should be avoided. Compliance aids and once-daily dosing may help minimise this.

Agents with complicated treatment schedules may be unsuitable and this may influence the choice of therapy, for example, calcium and vitamin D for osteoporosis prophylaxis rather than Didronel PMO or alendronate. Patients with dementia are vulnerable to falls, which may result in fractures, and drug treatments such as long-acting benzodiazepines may also contribute to this problem.

The detrimental effect on patients of not treating co-existing problems also needs to be avoided. For example, appropriate treatment of pain and palliative care, including pressure sore prevention and wound management, is essential, despite the difficulties with assessment where communication is impaired.⁹⁸⁻¹⁰⁰

This article was written before publication in January, 2001, of the NICE guidance on the use of cholinesterase inhibitors for the treatment of Alzheimer's disease.⁸ Some of the suggestions made in the article may have been superseded by these guidelines.

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