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Drug treatment for people with dementia

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Dementia is an international problem of enormous significance. Over 820,000 people in the UK live with Alzheimer's disease (AD) and other dementias. The estimated cost of dementia to the UK economy is £23 billion per year — more than the cost of cancer and heart disease combined.[1]

This article will concentrate on the specific drugs developed over the past 15 years for the treatment of dementia but mainly for the treatment of AD. (A more general CME update on dementia was published in the August 2010 issue.[2])

Two classes of drugs are approved for specific use in the treatment of dementia:

- *Cholinesterase inhibitors* (ChEIs). Three of this class of drug (donepezil, rivastigmine and galantamine) are approved for use in mild to moderate dementia in AD. Rivastigmine is also approved for mild to moderate dementia in Parkinson's disease (PD).
- *N-methyl-D-aspartate (NMDA) receptor antagonist.* One drug, memantine, is licensed for use in moderate to severe dementia in AD.

Alzheimer's disease

Cholinesterase inhibitors

Changes in the cholinergic system in AD have been known for over 25 years. A number of therapeutic approaches have tried to stimulate the cholinergic system but ChEIs are the only compounds to have shown consistent efficacy in clinical trials. ChEIs block the hydrolysis of acetylcholine at the synapse, increasing its availability to muscarinic and nicotinic receptors. All three ChEIs are active against acetylcholinesterase, the principal form of the enzyme. Rivastigmine is also active against butyrylcholinesterase whilst galantamine appears to be an allosteric modulator of nicotinic receptors in animal models. It has been suggested that these differences may lead to different clinical effects but this has never been convincingly demonstrated.

Side effects. The principal difference between the three compounds appears to be in the frequency and type of adverse events.[3] The main side effects are gastrointestinal (GI), particularly nausea, vomiting and diarrhoea. Donepezil is generally the best tolerated (with the simplest dosing schedule and commencing immediately with a therapeutic dose), followed by galantamine and then rivastigmine (GI side effects are more common in women). However, individuals vary as to which drug they tolerate best and adverse events can be minimised by careful dose titration. Rivastigmine is now available as a skin patch which reduces the risk of adverse GI side effects.

N-methyl-D-aspartate receptor antagonist

Glutamate may also be important in the pathogenesis of AD for a number of reasons, including its activity at the N-methyl-D-aspartate (NMDA) receptor which is capable of long-term potentiation and which is probably a prerequisite for memory. Memantine is an uncompetitive moderate-affinity antagonist at the NMDA receptor with strong voltage dependency and rapid blocking and unblocking kinetics. It restores glutamatergic neuronal transmission to a physiological level and prevents the effect of tonic pathologically elevated levels of synaptic glutamate that may lead to neuronal dysfunction.[4]

Current therapeutic regimens

Current drug treatments for AD and their dosing regimens are shown in Table 1. There is type 1a evidence for the efficacy of all three ChEIs in the treatment of mild to moderate AD and for the efficacy of memantine in the treatment of moderate to severe AD.[3] There is type 2b evidence to support the switching of one ChEI to another if the first is not tolerated or is ineffective, and for adding memantine to a ChEI.[3]

Cost-effectiveness

The clinical significance of the benefits from these drugs has been questioned, much of the debate having arisen following the assessment of their cost-effectiveness by the National Institute for Health and Clinical Excellence (NICE). Issues have been raised about the appropriateness of the outcome measures used in clinical trials, and how cost-effectiveness can be assessed in a chronic neurological disorder like AD where the disease has major implications not only for the patient but also for the family and society.

It has also been difficult to make an accurate assessment of the true cost of AD. Cost estimates vary widely according to the assumptions made and whether the full costs of the disease are being considered or only those borne by health services.

National Institute for Health and Clinical Excellence recommendations

In 2001, NICE recommended the use of the three ChEIs in patients with mild to moderate AD, but this advice was

Table 1. Current drug treatments for Alzheimer's disease. Registered indications in the UK.

Drug	Main mechanism of action	Mild MMSE 20–30	Moderate MMSE 10–19	Severe MMSE <10	Dosing
Donepezil (Aricept®)	AChEI	+	+	−	5–10 mg od
Rivastigmine (Exelon®)	AChEI	+	+	−	3–6 mg bd 4.6–9.5 mg skin patch/24 h
Galantamine (Reminyl®)	AChEI	+	+	−	8–24 mg bd or od
Memantine (Ebixa®)	NMDA antagonist	−	+	+	5–20 mg od

Donepezil: standard tablet and orodispersible tablet.
Galantamine: standard tablet and solution (both bd) and sustained-release capsule (XL od).
Rivastigmine: capsules and oral solution bd, transdermal skin patch od.
Memantine: tablets and drops od.

AChEI = acetylcholinesterase inhibitor; MMSE = Mini-Mental State Examination (maximum score 30); NMDA = N-methyl-D-aspartate (glutamate).

revised in November 2006 (amended September 2007 and August 2009).[5] The revised guidance suggested that the three ChEIs are cost-effective only in people with moderate AD, usually defined by a Mini-Mental State Examination (MMSE)[6] score between 20 and 10 (the MMSE is the most widely used brief cognitive assessment with a maximum score of 30). The NICE 2006 guidance recommended that memantine should be made available as part of well designed clinical studies or for patients already being treated with the drug.

These recommendations were extremely controversial, particularly the suggestion that people with mild AD need to wait until they are worse before being treated with ChEIs. This is in contrast to other recommendations[7] suggesting that ChEIs should be used as early as possible in AD.

NICE has recently re-evaluated the four drugs and issued a revised appraisal document likely to be adopted in early 2011. The revised recommendations suggest that treatment should be initiated by a specialist and that the three ChEIs are indicated within their licensed indications for mild to moderate AD. Furthermore, memantine is indicated within its licensed indication for people with moderate AD who are intolerant of or have a contraindication to ChEIs and for people with severe AD.[8]

The Mini-Mental State Examination

AD is a complex condition affecting not only memory and cognition but also performance of everyday activities, together with significant behavioural and psychological symptoms including agitation, aggression and psychosis. The MMSE is frequently used as the main estimate of cognitive change, but it has marked floor and ceiling effects and there are problems with test/retest reliability. The rate of change on the MMSE varies according to the starting score: for example, those with an initial MMSE score between 20 and 24 showed deterioration of 1–2 points per year but those with scores between 8 and 12 deteriorated by more than 5 points per year.[3]

In a chronic progressive condition like AD improvements in symptoms or stabilisation are important potential benefits but equally so is less than expected decline. This has been demonstrated for both donepezil and memantine. Using a definition of marked clinical worsening for a subject showing any cognitive decline plus any decline in both activities of daily living and global function, 30% of patients on placebo showed clinical worsening in comparison with only 14% of those on donepezil.[9] For memantine, 21% of patients showed

Key points

- Three cholinesterase inhibitors (donepezil, galantamine and rivastigmine) are licensed and effective in the treatment of mild to moderate Alzheimer's disease (AD)
- A N-methyl-D-aspartate (NMDA) receptor antagonist, memantine is licensed and effective for the treatment of moderate to severe AD
- Whilst improvement or stabilisation are important potential benefits from drug treatment, less than expected decline is also worthwhile, and has been demonstrated for both donepezil and memantine
- Cholinesterase inhibitors (ChEIs) and memantine may be of potential benefit in dementia with Lewy bodies (DLB), including for neuropsychiatric symptoms, and in dementia associated with Parkinson's disease
- Antipsychotic medications may be dangerous in people with DLB and should be avoided

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a significantly greater degree of worsening on placebo in comparison with 11% on memantine.[10]

This does of course mean that it may be difficult in an individual patient to decide whether or not drug treatment is beneficial. If appropriate, therapy may be withdrawn for a short period or the dose reduced to see if there is any change in the patient's condition.

Vascular dementia

Vascular dementia (VaD) is the second most common cause of dementia. It is a heterogeneous condition including single large infarcts, multiple small infarcts caused by emboli, strategically located lesions and diffuse white matter changes associated with chronic hypoperfusion.[11] There are no specific licensed treatments for VaD, so it is important to focus on reducing the underlying cardiovascular risk factors and any associated symptoms.

Drug therapy

A number of studies have been carried out with the currently available drugs for AD. A recent meta-analysis[12] included all VaD clinical trials in which donepezil, rivastigmine, galantamine or memantine were compared with placebo. ChEIs and memantine produced small benefits in cognition of uncertain clinical significance in patients with mild to moderate VaD, but generalisations about efficacy were difficult because of the heterogeneity of the patients. It is however appropriate to consider ChEIs or memantine in patients who have a mixed picture of dementia with both AD and VaD.

Parkinson's disease dementia

Although PD is predominantly a movement disorder, other impairments frequently develop including psychiatric problems such as depression and dementia. Rivastigmine is the only drug licensed for use in mild to moderate dementia in PD. The NICE 2006 guideline on PD[13] concluded that, although cholinesterase inhibitors have been used successfully in individual people with PD dementia, further research is recommended to identify those patients who will benefit.

Dementia with Lewy bodies

There is considerable overlap between the clinical and neuropsychological presentation of PD dementia with that of dementia with Lewy bodies (DLB). Visual hallucinations and visuoperceptual deficits are common to both, together with fluctuating attention.

The combination of cognitive, neuropsychiatric, motor and autonomic features in DLB causes considerable functional decline that may be more marked than in AD. Treating neuropsychiatric features such as hallucinations may exacerbate parkinsonism, while the use of antiparkinsonian medications may exacerbate psychosis. Subjects with DLB do not respond as well to antiparkinsonian medication compared with PD subjects. Nevertheless, recent studies suggest that around a third of subjects with DLB obtain a good motor response to L-dopa, although it is important to monitor side effects.[14] The medication should be introduced at low dose and the dose increased slowly, avoiding high doses. Other antiparkinsonian medications should be used with extreme caution because of the likelihood of inducing confusion and psychosis.[14]

There is type 1a evidence to support treatment with ChEIs in DLB, including for neuropsychiatric symptoms.[3] More recently, there has also been preliminary evidence for the benefit of memantine on cognition and clinical global impression of change in subjects with either DLB or PD dementia.[15]

Other dementias

Classification of frontotemporal dementia (FTD) is becoming more complex. There are also a number of other important causes of dementia, including progressive supranuclear palsy, corticobasal degeneration, prion disease and Huntington's disease. At present there is little evidence for the efficacy of ChEIs or memantine in any of these conditions, and worsening of behavioural symptoms in FTD by ChEIs has been reported.[16]

Posterior cortical atrophy[17] and logopenic progressive aphasia[18] are both thought to be atypical forms of AD, so it would be worth trying ChEIs or memantine in these conditions.

Use of antipsychotic drugs in people with dementia

There has been considerable publicity about the excessive use of antipsychotic drugs for the management of behavioural symptoms in dementia. This was highlighted in the recent Department of Health report[19] which estimated that at least 180,000 people with dementia are being prescribed antipsychotics each year. There have been a number of regulatory warnings about the risks of such therapy in people with dementia. It is estimated that there are an extra 1,800 deaths a year in the UK because of antipsychotic drug use, together with an additional 1,620 cerebrovascular adverse events (about half of which are severe).

Risperidone is the only drug specifically licensed for use in dementia, and only for short-term (up to six weeks) treatment of persistent aggression in moderate to severe AD unresponsive to non-pharmacological approaches and when there is risk of harm to the patient or others.

DLB patients may show severe sensitivity to neuroleptic drugs such as the atypical antipsychotics and fatal reactions have occurred.[20] Visual hallucinations are a common, sometimes early, feature of DLB. It is therefore important that physicians are aware of the need to avoid neuroleptic drugs in these patients.

Management of medical comorbidity in people with dementia

It is easy, but a mistake, to assume that all problems arising in people with dementia are due to the dementia.[21] Most people with dementia are older and likely to have other medical conditions, both acute and chronic. Problems such as incontinence should still be investigated and treated as appropriate,

rather than assuming this is an inevitable consequence of the dementia. Such an approach can make a significant difference to the quality of life for people with dementia and their families and carers.

Dementia is a significant independent determinant of non-treatment with aspirin or warfarin when otherwise indicated for the prevention of recurrent stroke.[22] However, there is no good reason to avoid anticoagulant therapy in an older person with dementia with a condition such as atrial fibrillation, providing there is no major risk factor and satisfactory compliance seems likely, for example if they live with a caring relative. Decisions should be made on a case by case basis.[21]

Overview

A general overview of drug treatment for dementia is shown in Table 2. Table 3 lists examples of the drugs most likely to cause acute confusion and which should be avoided in people with dementia if possible.

Table 2. Overview of drug treatment for dementia.

- Assess the patient with a possible dementing disorder carefully, including formal screening instrument (eg MMSE)
- If *cognitive impairment*, consider:
  - other relevant conditions (eg hypertension) and medications: treat as appropriate and review all medication (see Table 3)
  - depression: treat as appropriate and review
  - laboratory investigations for secondary causes and CT/MRI scan: if abnormal, treat appropriately and review
- Establish that the patient has dementia
- Establish the most likely type of dementia
- If *vascular dementia*, consider sources of emboli (eg carotid disease, AF)
  - if AF, consider anticoagulation
  - give low-dose aspirin (unless contraindicated)
- If *dementia with Lewy bodies*, consider:
  - L-dopa for parkinsonian symptoms
  - ChEIs (and possibly memantine), especially for visual hallucinations
  - do not use neuroleptics
- If *Alzheimer's disease*, consider ChEIs. Before commencing, choose specific target symptoms with patient and caregiver and measure MMSE. Titrate to maximum dose according to side effects and benefits
  - if problems with first ChEI, consider switching to another ChEI or memantine
  - if ChEIs poorly tolerated or contraindicated, consider memantine
  - as disease progresses, consider switching to memantine or adding memantine to the ChEI, particularly if the patient is developing agitation
  - monitor the patient's progress 6-monthly
  - if stopping drug treatment, consider dose reduction rather than complete withdrawal, and be aware that the patient may deteriorate and medication need to be restarted

AF = atrial fibrillation; ChEI = cholinesterase inhibitor; CT = computed tomography; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging.

Table 3. Examples of drugs that can cause acute confusion (use with care in people with dementia).

Drugs with anticholinergic properties	Other drugs
Tricyclic antidepressants	Alcohol
Antihistamines	Benzodiazepines
Antispasmodics	Narcotic analgesics
Antipsychotics	Trazodone and other antidepressants
Antiparkinsonian drugs	Lithium carbonate
Oxybutynin	Digoxin
	Diuretics
	Anticonvulsants
	Cimetidine
	Steroids
	Indomethacin and other non-steroidals
	Antihypertensives (? especially calcium-channel blockers)

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