

Diagnostic work up and treatment of dementia

Dementia is defined as a progressive decline in cognitive function, with memory being especially affected.¹ It is associated with a progressive decrease in the patient's intellect accompanied by reduced emotional control and a deterioration of social functioning. The acquired cognitive and behavioural impairment will eventually become of sufficient severity that it interferes with social and occupational functioning of the patient.

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There are currently approximately 750,000 people in the UK with dementia and this will increase to over one million people by 2025.² The cost of providing care to patients with Alzheimer's disease in the USA reached \$144 billion last year with 5.3 million people being affected.³ As with many long-term medical conditions dementia affects a large number of people as well as the patient and can result in significant strain within families. Recently, there has been political reform around the long term care (LTC) of those with dementia. Therefore, it is clear that dementia is now a major social, political, economic and medical issue.

Making a diagnosis

A patient will typically present to their GP after they or their family/friends notice changes in cognitive function. A common presentation is memory loss that would typically

affect short-term memory. Additional presenting symptoms include dysphasia (deterioration of language/speech), apraxia (perception and comprehension) and agnosia (inability to recognise objects).⁴ There are often reservations and concerns about clinicians confirming an untreatable condition. However, it is important that a diagnosis is made as early as possible as this enables patients and their families to adjust to the condition and prepare for the future.

The GP typically will carry out a range of assessments and examinations. Firstly, the doctor needs to ensure that the patient has evidence of a chronic cognitive decline and that the patient has a normal conscious level.⁴ If this is not the case then the differential diagnoses of an acute confusional state and delirium are important to consider.⁴ The GP needs to establish a good background picture of the patient to assess what the potential cause

of the dementia may be and what the appropriate next step should be.³ A comprehensive history is important as the past medical history (PMH) may yield potential insights into the cause of the patient's dementia. For example, Korsakoff's alcohol induced dementia would feature prominently in the differential diagnosis of a patient with an established history of alcohol abuse. A PMH of previous carcinoma may merit hospital investigations for potential metastatic disease. Finally, a family history of dementia may raise the spectre of genetic factors (including APOE or presenilin genes).

A general physical examination and baseline tests is important to attempt to exclude any reversible causes of cognitive impairment eg. thyroid function tests, full blood count, liver function tests, calcium, renal function, and vitamin B12 levels (Table 1).

Table 1: Reversible causes of dementia symptoms to be excluded

Low T4 and low thiamine (especially in alcoholics)
Low folate
Subdural haematoma (acute or chronic)
Syphilis or HIV (cryptococcosis)
Parkinson's disease
Tumours (primary or secondary)

There are two important cognitive assessments that can be carried out by GPs to assess a patient's cognitive function. The General Practitioner Assessment of Cognition (GPCOG) test is scored out of nine,⁵ and questions assess a patient's memory as well as a practical task. The components of the GPCOG test are outlined on Table 2.⁵

The Mini Mental State Examination (MMSE) is useful in

establishing whether a patient has a degree of cognitive impairment.⁶ The MMSE takes around 5-10 minutes to administer and assesses orientation in time and place (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), language (2 points) repetition (1 point) and interpreting complex commands (6 points).⁷ Scores below 25 out of 30 indicate a degree of cognitive impairment. Current NICE guidance advocates that after patients have had a primary care memory assessment and documented functional impairment, all patients be referred to the memory clinic and/or a structured group cognitive stimulation program.⁸ These programmes can provide practical advice and support for patients with a dementing syndrome. MMSE or GPCOG scores can also be used to chart the cognitive decline of patient and can be used to aid patient management decisions.¹

In clinical practice it can be difficult to distinguish between

the different types of dementia. However, there are variety of signs and symptoms that can be helpful in differentiating clinically between Alzheimer's disease, dementia with Lewy bodies (DLB) and vascular dementia. A patient with vascular dementia may have a history of vascular disease, transient ischaemic attacks or previous strokes.⁵ These patients may have a sudden decline of cognitive function as a result of a vascular event that can improve slightly over time but not to prior cognitive levels.⁴ Patients with DLB are typically more prone to have hallucinations or delusions with some sleep disturbance.⁶ One of the major considerations with patients with DLB is neuroleptic hypersensitivity.⁶ Neuroleptics are potent tranquillizers and may be prescribed for severe behavioural changes in patients with marked cognitive impairment including dementia. Symptoms of narcoleptic hypersensitivity include muteness, rigidity (Parkinsonism features) and neuroleptic malignant syndrome,

Table 2: GPCOG test components

Stage 1: Patient is interviewed by GP	Stage 2: Informant section
	Stage 2 has six questions that assess how the person is now compared to when they were well, for example 5–10 years ago.
Score of 9: no significant cognitive impairment and further testing is not necessary.	If the informant's score is less than 4 (out of 6), cognitive impairment is suggested.
Score of 5–8: more information is required. Proceed with Step 2, the informant section.	

which is autonomic nervous instability and cognitive instability due to exposure to neuroleptics.⁹ Despite some clinical clues it is not uncommon for patients not to have a clinically confirmed dementia syndrome. In these specific cases, the NICE dementia guideline recommends MRI scans.⁸

Following the diagnosis of significant cognitive dysfunction and referral to a specialist centre it is important to ensure that adequate community and social support is provided. This support varies between different Local Authorities but there are several important stages that enable an effective support network to be established for both patient and carers. Firstly, some NHS Trusts may suggest a short-term (3–7 days) admission to hospital to specifically assess the patient's 24-hour care needs. This information can be very important to the family and can affect whether they think LTRC needs to be considered and how confident they feel about the provision of long-term care. Community assessment by the social service department can help the family arrange the social care they need and is a mandatory arrangement for all patients who wish to have LTRC.

Current pharmaceutical options for patient care

There are currently no drugs that can cure Alzheimer's disease, DLB or vascular dementia. The main aim of treatment is symptomatic relief and slowing disease progression. There are two major classes of drugs that

are commonly prescribed to patients with dementia. Firstly, there is a range of drug treatments that have been developed to control the symptoms of patients with Alzheimer's disease. These drugs are expensive and can currently only be commenced by a consultant. The drugs are only effective for a short period of time after which the patient will experience rapid cognitive decline to the level of a patient who had not received the drug.¹⁰ Therefore, the drug has short-term but no long-term benefits so there are complex cost-benefit ratios that are discussed and reviewed by NICE as well as individual NHS Trusts.

Other drugs prescribed by doctors for patients with dementia are symptomatic. For example, occasional patients may benefit from short-term treatment with neuroleptic agents to help control serious behavioural symptoms.

Specific AD medications

Currently there are four drugs that are licensed for use in patients with dementia. Three of these drugs are based on the "cholinergic hypothesis" that suggests that there is a reduction in available acetylcholine (ACh) in patients with Alzheimer's disease.³ ACh is an important neurotransmitter that is important for the communication between nerve cells.¹⁰ Acetylcholinesterase inhibitors act to prevent the activity of the enzyme that degrades ACh in the brain. This subsequently increases the concentration of ACh in the brain and has been shown to help symptoms

of memory loss and slows the behavioural changes associated with Alzheimer's disease. There are three acetylcholinesterase inhibitors that are licensed for use in the UK. These are Aricept (donepezil hydrochloride), Exelon (rivastigmine) and Reminyl (galantamine). The choice depends upon the NHS Trust as well as the side effect profile of the drug on the patient. Importantly, a Cochrane review found almost one third (29%) of patients cannot take these anti-dementia drugs due to the gastrointestinal side effects such as nausea, vomiting and diarrhoea.¹¹

The other drug licensed for use in patients with dementia is Ebixa (memantine hydrochloride) that has an entirely different mechanism of action compared to the acetylcholinesterase inhibitors. The fundamental concept is that memantine acts to prevent excitotoxicity within neurones.¹² Neuronal excitotoxicity results from prolonged calcium influx that activates multiple enzymes such as proteases and phospholipases.¹³ The overactivation of enzymes damages cellular components within the neurone and can lead to neuronal death.¹³ Memantine blocks the action of glutamate by acting as an antagonist to the NMDA receptor where glutamate binds.¹² Glutamate is an important neurotransmitter involved in memory and learning.¹⁴ The signalling of glutamate is disturbed in Alzheimer's disease and the aim of memantine is to restore glutamergic signalling to physiological levels. Patients using memantine can have significant cognitive benefits but, like acetylcholinesterase drugs,

not all patients will respond to treatment.¹⁵ In addition, the drug is contraindicated in patients with renal failure defined as a creatinine clearance below 50mls/min.¹⁵

The National Prescribing Service (NPS) (Australia) after reviewing memantine concluded that memantine treatment was associated with modest overall improvements in patients with Alzheimer's disease.¹⁶ The report found that patients with severe dementia or moderate dementia (if intolerant to acetylcholinesterase inhibitors) be started on the drug and reviewed after six months.^{8,16} The NPS, along with NICE, have called for head-to-head trials between memantine and acetylcholinesterase inhibitors in order to determine which drug therapy is the most effective.

Neuroleptics and symptomatic drugs

Patients with dementia can develop behavioural problems ranging from aggression to agitation and psychiatric disorders. Firstly, the patient should be assessed to see if psychological treatment could improve the patient's symptoms. For example, a patient may become aggressive because of excessive noise or not being able to go outside in some nursing home settings. It is always desirable to implement a non-pharmaceutical intervention if possible.¹⁷ However, this is not always possible and there are a variety of drugs that are used to control the disturbing symptoms experienced by a selection of dementia patients.

Neuroleptics, also known as

anti-psychotics, can be used to try to control symptoms of aggression and psychiatric symptoms in dementia patients.¹⁷ Risperidone and aripiprazole are the most commonly prescribed in the UK and USA and are now licensed for use in dementia patients.¹⁷ The Alzheimer's Society UK suggests that these drugs only be used for three months as there may well be some improvement in patient aggression and psychiatric symptoms over this time frame.¹⁵ However, longer-term trials show a more limited benefit with increased side effects.¹⁷

Long-term usage of neuroleptics is associated with an increased risk of developing cardiovascular disease and strokes.¹⁸ Furthermore, there is evidence to suggest that long-term use may hasten cognitive decline.¹⁹ There are other significant side effects associated with these drugs including anticholinergic effects (such as tachycardia and an ileus), hypotension and prolongation of the QT interval.¹⁸ Therefore, the use of these drugs should be used with caution, over a short time period and only in conjunction with community patient support.

There is emerging evidence that anti-convulsant and anti-depressant drugs can be used to treat agitation and aggression.^{20,21} As discussed anti-psychotic drugs have a variety of side effects and it is thus desirable to use other drugs with a reduced side-effect profile.

For example, in one study where patients were prescribed risperidone, 50% of patients experienced significant improvement in their symptoms but had a 50% chance of

developing extra pyramidal side effects such as akinesia and akathisia.²²

The anti-convulsant gabapentin alters the activity of important neurotransmitters that are thought to play a role in the behavioural changes in Alzheimer's disease.²⁰ These include gamma-aminobutyric acid (GABA), serotonin and glutamate.²⁰ Gabapentin may be an appropriate drug to use in elderly patients who are likely to be on several drugs as it is not metabolised by the liver and therefore the metabolism of other medicines remains unaffected.²⁰

There is a wide range of medications that can be used to try and address the behavioural changes that can arise in patients with dementia. The use of these drugs is a complex subject. The Alzheimer's Society indicated their concern about the overuse of these medications in a letter to the Department of Health.²³ They argued that there was a significant body of evidence suggesting that neuroleptics are "only appropriate in very limited situations".²³

The Society referred to a Government funded review by Professor Sube Banerjee indicating that approximately 150,000 patients are inappropriately prescribed antipsychotic drugs with this resulting in an extra 1,800 deaths per year.²⁴ There are thus important balances that need to be achieved between the potential therapeutic benefits and side effects of these drugs. Finally, it also emphasises the importance of trying to address patient symptoms with lifestyle and environmental changes or support as this can be of huge benefit to the patient.²³

Conclusion

In conclusion, it is clear that dementia is an emotive issue and one with no magic medical bullet. Although there is hope that current research aimed at curing or limiting Alzheimer's disease by augmenting the removal of amyloid plaques, will prove fruitful this is years away at best.²⁵ To try and enable a patient to experience 'best care', emphasis must be placed on a multi-disciplinary approach. Hospital specialists, GPs, social care services, private care agencies and family members need to communicate well to try and assess the patient's care and medical needs and discuss what can be done in the future for an effective transition of care.

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