Management of Alzheimer's disease patients in Lancaster Memory Assessment Clinic

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia. It is a serious brain disorder that impacts on daily living through memory loss and cognitive decline. Dementia affects one in 14 people over the age of 65, one in six over the age of 80 and over half of those over 90 years. Recent figures suggest that there are 26 million people worldwide living with dementia. In the UK, 2012 figures suggest that there are 800,000 people in the UK suffering from dementia, out of which 17,000 people were under the age of 65.⁽¹⁾ AD accounts for 55%. Other types and frequency of dementia include vascular dementia (20%), dementia with Lewy bodies (10%), fronto-temporal dementia (8%), Parkinson's dementia (2%), and other classification of dementia (5%). Table 1 describes brain regions affected by different types of dementia.

AD is a degenerative disease of the brain with unknown aetiology with characteristics, neuropathological and neurochemical features. It is usually insidious in onset and develops slowly but steadily over a period of years. This period can be as short as 2-3 years, but can be longer. Onset can be in mid-life or even earlier in the case of AD with early onset, but incidences are higher in later life. Generally in those who develop AD before the age of 65 there is family history of similar dementia, having rapid course and features of temporal and parietal lobe damage, such as aphasia, agraphia, alexia and apraxia, occur relatively early in the course of dementia in most cases. There is also marked multiple disorder of higher cortical functions such as memory, orientation, attention, concentration, judgment ability, executive function, etc. There is a marked reduction in neurons in hippocampal, substantia innominata, locus coeruleus and temporoparietal and frontal cortex. There is appearance of neurofibrillary tangle plaques

largely of amyloid and so definite progression in their development, although plaques without amyloid also can exist. Neurochemical changes show marked reduction in enzyme choline acetyltransferase, in acetyl choline itself and in other neurotransmitters and neuromodulators.

Amyloid protein precursor (APP) gene: risk factor for early onset AD

APP has an autosomal dominant pattern of inheritance that is fully penetrant. Each child of an affected individual has a 50% chance of inheriting the gene mutation. AD will develop in any such affected individual surviving the age of risk of 40-65 years. The APP gene and its mutations have been found in only 43 families worldwide.

The primary risk factors for AD are age, family history and genetics⁽²⁾ – such as in early-onset AD, generally associated with specific gene mutation (the APP gene found on chromosome 21, the PSI gene on chromosome 14, and the PS2 gene on chromosome 1).

Conversely, *late-onset* AD has a different genetic basis. The gene ApoE (Apolipoprotein E) on chromosome 19 has three alleles of relevance: ApoE₂, ApoE₃ and ApoE₄. Of these, the allele ApoE₄ is associated with a recognised higher risk of AD.

While there is an underlying genetic predisposition, the progression to overt disease status is influenced, as it is in many other conditions, by environmental factors. Maintenance of a healthy heart and avoidance of high blood pressure, heart disease, stroke, diabetes and high cholesterol, tobacco, and excess alcohol, along with a healthy lifestyle (including exercising both body and mind), can help in delaying onset, or help to maintain the condition as only minimal cognitive decline.

Dementia type	Main brain areas affected	Characteristic symptoms caused
AD	Cortex, hippocampus	Cognitive decline, personality changes
Lewy body variant of AD	Neocortex, thalamus, hippocampus, frontal cortex	Cognitive and attentional deficits, hallucinations, delusions, depression, sleep disturbance
Parkinson's disease dementia	Neocortex, thalamus, basal forebrain, hippocampus, frontal cortex	Hallucinations, cognitive deterioration, attentional deficits, impaired temporal judgements, poor sequencing
Subcortical vascular dementia	Frontal cortex	Executive dysfunction, attentional deficits, behavioural problems
Fronto-temporal dementia	Areas of frontal and temporal cortex	Behavioural problems (lose their inhibitions, socially inappropriate behaviour in language and action) Lose sympathy or empathy Obsessional behaviour Semantic dementia – speech is fluent but people begin to lose their vocabulary and understanding of what objects are Difficulty in finding the right word Progressive non-fluent aphasia – slow hesitant speech, errors in grammar; impaired understanding of complex sentences

Table 1 Brain regions affected by neurodegenerative and cholinergic changes in patients with different dementia types

PATHOPHYSIOLOGY

The pathogenesis of AD is poorly understood. There are a number of pathways believed to contribute to neuronal dysfunction and death. These include:

- decreased acetylcholine synthesis and impaired cholinergic function
- glutamatergic excitotoxicity
- direct toxicity of β -amyloid peptide
- mitochondrial dysfunction
- increased oxidative stress
- activation of metabolic pathways in the cell leading to programmed cell death – 'apoptosis'
- release of inflammatory mediators
- impaired calcium signalling and regulation

Increasing evidence suggests that selective neuronal loss in neurodegenerative disease involves activation of cysteine aspartyl proteases (caspases) which initiate and execute apoptosis. In AD, both extracellular amyloid deposits and intracellular amyloid β protein may activate caspases, leading to cleavage of nuclear and cytoskeletal proteins, including tau protein. Proteolysis of tau may be critical to neurofibrillary degeneration, which correlates with dementia.

These pathways present new opportunities in developing novel AD therapies.

DIAGNOSIS

International Classification of Disease 10th revision (ICD10) criteria⁽³⁾ for diagnostic guidelines for dementia in AD include evidence of a decline in memory, which is most evident in the learning of new information, although in more severe cases the recall of previously learned information may be also affected. The impairment applies to both verbal and non-verbal material. The decline should be objectively verified by obtaining a reliable history from an informant, supplemented, if possible, by neuropsychological tests or quantified cognitive assessments.

ICD10 criteria also include:

- insidious onset with slow deterioration
- absence of clinical evidence or finding from special investigation to suggest that mental state may be due to other systemic or brain disease which can induce dementia, such as hypothyroidism, hypercalcaemia, vitamin B12 deficiency, niacin deficiency, neurosyphilis, normal pressure hydrocephalus or subdural haematoma
- absence of sudden onset or of neurological signs of focal damage, such as hemiparesis, sensory loss, visual field defect and incoordination occurring early in the illness

Late-onset AD over the age of 65 (usually in the late 70s) shows slow progression, usually with memory impairment being the main symptom.

Dementia produces decline in intellectual functioning and some interference with personal activities of daily living, such as washing, dressing, eating, personal hygiene, excretory and toilet

activities. The above symptoms and impairment should have been evident for at least six months for a diagnosis of dementia.

THE ASSESSMENT PROCESS AT LANCASTER MEMORY ASSESSMENT CLINIC

Lancaster Memory Clinic was instituted in 1997 to address issues related to the noticeable rise in an aging population,⁽⁴⁾ who were displaying signs of cognitive loss which resulted in an insidious loss of personality and memory. The population of Lancaster is 141,000, out of which 25,300 are above the age of 65 years.⁽⁵⁾ The rate of referral significantly increases every year. The analysis of referrals, and the evolution of the clinic, has been detailed previously in this journal.⁽⁶⁾

New referrals in 2012 were 521, increasing to 559 in 2013. In January 2014, we received 63 new referrals, which is double the number from 2012. We have observed that the referral rate has increased significantly in the last four months.

Lancaster Memory Clinic was one of two clinics first accredited when the Memory Services National Accreditation Programme was established (2009) and is currently **accredited** as excellent.

Prior to a patient being seen by the clinic, the following information is expected from their general practitioner (GP) as per memory clinic protocol:

- brief information
- past medical history
- recent blood tests
- ECG
- details of medication

The patient also undergoes a computerised tomography (CT) head scan which is arranged at Lancaster Memory Assessment Clinic.

As previously reported (MBMJ 2011;6(4):110-12), CT imaging may demonstrate subtle changes of cortical atrophy that may support the diagnosis of dementia, but these changes need to be correlated with clinical findings

At Lancaster Memory Assessment Clinic, the patient is visited at home or at the clinic by a memory clinic nurse. The nurse will conduct a detailed questionnaire with the patient or carer about the person's cognitive problem which highlights the patient's cognitive problem, anxieties, mood and any other psychiatric symptoms if relevant and their ability to manage activities of daily living. The family history of the cognitive problem and relevant personal history (including alcohol/smoking habit, pre-morbid personality, hobbies, interests) and past psychiatric illness and treatment is also noted.

A number of psychometric tests are also offered:

- CAMCOG (Cambridge Cognitive) – cut-off score for cognitive impairment is 81/105
- ACE III (Adenbrookes) – cut-off score for cognitive impairment is 83/100
- MOCA (Montreal Cognitive Assessment) – cut-off score is less than 26/30
- GDS (geriatric depression scale) – a patient who appears low in spirit/depressed will be assessed if there is any underlying depressive illness. A score above 6/15 signifies subjective feeling of depression
- DASS (depression, anxiety, stress, scale) is made up of 21 self-reported items, each of these rated on four points giving severity indicators for depression, anxiety and stress

Then, a clinical interview with a doctor occurs, who takes into account all of the above information and the results from the CT head scan. Some patients who score above the cognitive impairment cut-off score (ie ACE III score above 90/100, or 87/105 in CAMCOG) yet suggest cognitive problems in clinical information, are then referred to a clinical psychologist for further and more detailed psychometric tests.

INITIAL TREATMENTS⁽⁷⁾

At Lancaster Memory Assessment Clinic, an AD patient will be prescribed either acetyl cholinesterase inhibitor or memantine. The doctor will initiate the medication and the memory clinic nurse will titrate medication and at the end of three months will request the patient's GP to take over prescription as per Shared-Care Protocol and the patient will then be monitored in a nurse-led clinic. Initially, it was six monthly but now the present arrangement is once a year (assessment by memory clinic nurse).

- information on memory tips (booklet), prepared at our Memory Assessment Services
- inform patients of their obligation to inform DVLA and car insurance company about their diagnosis. Patient's suitability to drive is also assessed and information given appropriately
- information on Lasting Power of Attorney includes property and finance (previously known as Enduring Power of Attorney) and welfare for health decision and future social care
- assessment includes risk identification and support network

- support from occupational therapist (OT) home assessment (if needed) and installing home aids as necessary
- also give information on support services, ie Day Centre, input from Alzheimer's Society, other voluntary organisations, carer's services, etc

If it is suspected that the diagnosis is mild cognitive impairment due to aging, as opposed to a diagnosis of dementia, the patient will be discharged from clinic with advice to carer to monitor cognitive functioning skill and if there is a deterioration then to approach their GP for re-referral to the Memory Assessment Clinic.

MANAGEMENT OF AD

There are no drug treatments available that can provide a cure for AD. However, medicines have been developed that can improve symptoms and slow down disease process.

There are two main types of medication used to treat AD, which work in different ways:

1. Acetyl cholinesterase inhibitors, eg donepezil hydrochloride (Aricept), rivastigmine (Exelon) and galantamine (Reminyl)
2. NMDA receptor antagonists, eg memantine (Ebixa)

ACETYL CHOLINESTERASE INHIBITORS

Research has shown that the brains of people with AD show a loss of nerve cells that use acetylcholine as a chemical messenger. The loss of this nerve cell is related to the severity of symptoms that people experience.

Donepezil, rivastigmine and galantamine prevent an enzyme acetylcholinesterase from breaking down acetylcholine in the brain, which leads to increased concentration of acetylcholine, leading to increased communication between the nerve cells that use acetylcholine as a chemical messenger; which may in turn temporarily improve or stabilise symptoms of AD. All three cholinesterase inhibitors work in a similar way, but one might suit an individual better than the others. Rivastigmine also inhibits BuChE (butylcholinesterase), which is also involved in the breakdown of acetylcholine (ACh) in the brain and dual inhibition may lead to greater, broader efficacy, as well as greater potential for disease modification. Also, only rivastigmine appears to show brain region-selectivity, particularly regions involved in attention and behaviour. This selectivity is due to preferential inhibition of the G1 form of AChE and, probably, also BuChE. Cholinesterase inhibitors that lack preferential selectivity for particular isoforms may provide less targeted actions.

The National Institute for Care and Health Excellence (NICE) recommends that acetylcholine esterase inhibitors treatment is started by a doctor who specialises in the care of people with dementia at a local centre, provided there are no contraindications and after ECG measurements have been taken if required. If there are any cardiac risk factors present, eg cardiac conduct disorder, bradycardia, etc, then the Royal College of Psychiatrists guidelines should be followed, as shown below in figure 1.

Suggested guidelines for managing cardiovascular risk prior to and during treatment with acetylcholinesterase inhibitors in Alzheimer's disease. bpm, heartbeats per minute; the 'drug' means the chosen AChE inhibitor.

Fig. 1 Suggested guidelines for managing cardiovascular risk prior to and during treatment with acetylcholinesterase inhibitors in Alzheimer's disease. bpm, heartbeats per minute; the 'drug' means the chosen AChE inhibitor.

Figure 1 Suggested guidelines from the Royal College of Psychiatrists

(reproduced with kind permission of the RCPsych from Rowland JP, Rigby J, Harper AC, Rowland R. Cardiovascular monitoring with acetylcholinesterase inhibitors: a clinical protocol. *Adv Psychiatr Treat* 2007;13:178-84)

NMDA RECEPTOR ANTAGONIST (MEMANTINE)

Seventy per cent of all excitatory neurons use glutamate as neurotransmitter. Therefore, the signal transduction via glutamate is essential for intact execution of all CNS functions, especially those of cognitive processes.

Memantine blocks glutamate. Glutamate is released in excessive amounts when brain cells are damaged by AD and this causes the brain cell to be damaged further. Memantine can protect brain cells by blocking these effects of excess glutamate. Figures 2 to 4 show glutamate neurotransmitter behaviour in a normal situation, in a patient with AD, and how memantine acts on the excess glutamate. (Reproduced with kind permission of Lundbeck.)

The following conditions can be made worse by memantine, so need to be excluded before treatment is started:

- kidney disfunction
- liver disfunction
- epilepsy
- cardiac failure
- ischaemic heart disease
- constipation
- dizziness or excess sedation

Also, it is important to note any drug interactions with memantine:

- cimetidine
- ranitidine
- quinine
- warfarin
- any oral solutions that contain sorbitol

It follows that patients receiving treatment need monitoring for:

- blood pressure
- constipation
- dizziness
- falls
- any psychiatric symptoms

NICE currently recommends that donepezil, rivastigmine and galantamine are available as part of NHS care for people with mild to moderate AD.

Between 40-70% of people with AD benefit from acetyl cholinesterase inhibitor treatment, but it is not effective for everyone and may improve symptoms only temporarily, between 6-12 months in most cases. According to an Alzheimer's Society survey of 4,000 people, those using this treatment often experience improvement in motivation,

Interactions	Mechanism	Potential sequelae
AChEs + anticholinergics	Decrease ACh in CNS	Cognitive worsening, delirium
AChEs + beta blockers	Vagal stimulation; sympathetic block	Bradycardia, syncope
AChEs + cholinergics	Increases ACh in peripheral nervous system	Cholinergic crisis; hypersalivation, abdominal pain, diarrhoea, etc
AChEs + antipsychotics (rare)	Increase ACh / decrease dopamine in striatum	Parkinsonian syndrome, rigidity
Ginkgo biloba + warfarin	Antiplatelet aggregation & anticoagulation	GI bleeding, haematuria, subcutaneous ecchymosis
Table 2 Drug-drug interactions: (acetyl cholinesterase inhibitors and other drugs) ⁽¹⁰⁾		

anxiety level and confidence, in addition to daily living, memory and thinking. It is not clear whether the cholinesterase inhibitors bring benefit for behaviour symptoms such as agitation or aggression. Trials showed that these drugs and memantine bring some relief from the carer's perspective – drug treatments for AD.⁽⁸⁾

Memantine is licensed for treatment of moderate to severe AD. There is evidence that memantine may also help behavioural symptoms such as aggression and agitation.

There are a few studies that have concluded that taking donepezil with memantine is more effective than taking donepezil alone in moderate to severe AD.⁽¹⁾ At the same time, if a patient stops taking donepezil in order to try memantine their symptoms could become worse, which could then make it difficult to assess suitability for memantine. The latest 2011 guidance from NICE does not recommend the combination treatment.⁽⁹⁾

There is evidence that anticholinergic drugs cause cognitive worsening and possible delirium, so it is important to be aware if other drugs are being concomitantly prescribed that also have anticholinergic activity.

Area of cholinergic activity		Side effects	Reported with rivastigmine	Reported with donepezil	Reported with galantamine
Central	Hypthalamus (area postremus)	Gastrointestinal (nausea and vomiting)	+++	++	++
	Caudate nucleus	Extrapyrimal symptoms	+/-	++	+/-
	Brainstem (pons)	Sleep disturbances	+/-	++	+/-
	Medualla (cardiorespiratory centres)	Cardiovascular and respiratory	+/-	+	+
	Frontal/temporal lobe	Agitation	+	++	++
Peripheral	Peripheral inhibition	Bradycardia and ECG abnormalities	+/-	+	+
	Peripheral neuromuscular junction	Muscle cramps and weaknesses	+/-	++	+/-
	Bladder	Urinary incontinence	+/-	+	+/-
Table 3. Relationship of cholinergic activity at different central and peripheral sites to side effects reported with ChEs in the treatment of dementia. ⁽¹⁰⁾ Where cholinergic activity: +/- (little or none), + (mild), ++ (moderate), +++ (strong)					

Class	Examples
Antiarrhythmic	Disopyramide
Antiemetic	Metoclopramide – cyclizine (UK)
Antiparkinsonian	Benzotropine, trihexyphenidyl
Antipsychotic	Chlorpromazine, clozapine, olanzapine, pimozide, thioridazine
Antihistamine	Chlorpheniramine, cyproheptadine, diphenhydramine, hydroxyzine, promethazine
Gastrointestinal/urinary antispasmodics	Atropine, belladonna alkaloids, hyoscyamine, oxybutynin, copolamine, tolterodine
H2 histamine blockers	Cimetidine, ranitidine
Muscle relaxants	Cyclobenzaprine
Tricyclic antidepressants	Amitriptyline, imipramine, clomipramine, doxepin, protriptyline

Table 4 Medications with moderate to strong anticholinergic activity ⁽¹⁾

COMPONENTS OF A HEALTHY LIFESTYLE

Patients are also given guidance on the importance of a healthy lifestyle, as a healthy lifestyle can improve mental health and physical health.

An active social life

- become a volunteer
- join a club or social group
- take group classes (gym/community college)
- phone/email/Facebook
- know your neighbour
- quality time with family member/friend
- dance class

Participate in regular exercise

At least 30 minutes cardiovascular exercise (five times a week).

Healthy diet – 'Mediterranean Diet'

- omega 3 fats (food sources – cold water fish, such as salmon, tuna, trout, mackerel, sardines and fish oil)
- nuts, olive oil, whole grains, fish, occasional glass of red wine and a square of dark chocolate
- green tea (2-4 cups per day)
- also, the inclusion of Indian spices, such as turmeric (active ingredient is curcumin), cumin, fenugreek and mustard seeds, can help as part of a healthy diet

Mental stimulation

- learn something new, ie foreign language, sign language, music
- practise memorisation

- games, puzzles and riddles
- follow the 'road less travelled' – take a new route
- rearrange your computer file system
- vary your habits regularly to create new brain pathways

Quality sleep

- establish a regular sleep schedule
- ban television and computers from the bedroom
- relaxing bedtime ritual (take a hot bath, do some light stretches, write in diary/journal, dim light)
- quiet your inner chatter (when stress, anxiety or negative internal dialogue – get out of bed, try reading or relaxing for 20 minutes then back into bed)

Stress management

- lower your stress response with deep, abdominal breathing
- relaxing activities (eg walk in a park, playing with a dog, yoga, soothing bath)

FUTURE DEVELOPMENTS IN TREATMENT OPTIONS

There are a number of amyloid treatment strategies, eg:

- to remove amyloid deposits already laid down
- to prevent the A β formed from acting as a toxin
- to prevent production of A β

CONCLUSION

With patients' life expectancy increasing worldwide, more people are suffering from disease of age, particularly dementia over the age of 90 (one in two people suffer with dementia). Dementia is a progressive, irreversible and very debilitating disease, which as it progresses affects cognitive functions, activity of daily living and also causes changes in personality, mood and behaviour. This impacts on the spouse/carer's personal life also.

The National Dementia Strategy has three key steps to improve the quality of life for people with dementia and their carers:

1. To ensure better knowledge about dementia and remove stigma – need for better education and training for healthcare professions.
2. Early diagnosis with a view to support the person and their family with treatment as early as possible.
3. To develop a range of services that meet the changing needs of people with dementia and their carers in the future, such as involving their GP, working alongside mental health services, GP knowing how to spot the first signs of dementia and referring to dementia services in hospital, where people with dementia will get information and support as soon as possible, helping people with dementia to stay in their own home for longer.

Lancaster Memory Clinic's ethos is early diagnosis treatment (pharmacological and non-pharmacological) intervention with information, guidance on cognitive stimulation and other social stimulations and information on other support networks.

The following services we did have, but recently, due to changes in the structure, it appears there is some hold back at present, but hopefully they will restart again:

- post-diagnostic support group: which is for the patient, as some carers and patients struggle to come to terms with the diagnosis. This is a once-a-week session for six weeks in the community by the occupational therapist
- Memory Management Group: which is mainly for the vascular dementia patient, as there is no specific drug treatment from the Memory Clinic apart from guidance and information on keeping their cardiovascular system as healthy as possible. This is a one-to-one session, once a week for six weeks
- HOPE (helping occupational performance through engagement): which is for the carer – not more than eight carers in a group. This is also one session per week – total of seven sessions
- in addition to the above, there are also drop-in centres where the patient and carer meet other patients and carers. They share their experience and feel supported by healthcare professionals. At present, there is one drop-in session at the George Hotel in Torrisholme, which has been initiated over the last two years (once in two months) – healthcare professionals from the Memory Clinic as well as Alzheimer's Society staff are present, who can help patient and carer with any ongoing problems/difficulties in management. Another centre will start in Garstang in the near future
- there are also three day centres: Vale View (Lancaster), De Vitre House (Lancaster) and Altham Meadows (Morecambe). All run by Social Services
- in addition, some patients also have respite care for the weekend or one week every 3-4 months, depending on carer's needs

There are several studies ongoing, including drug trials for AD, and the government is also pressing for awareness of dementia and improving support networks to patients and their families.

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