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MANAGEMENT OF DEMENTIA

-  **The prevalence of dementia is increasing with the ageing population**
-  **Alzheimer's disease is the commonest type of dementia affecting up to 50% of patients with dementia**
-  **Management of dementia requires both a non-pharmacological and pharmacological approach**
-  **Acetylcholinesterase inhibitors are of benefit in mild to moderate Alzheimer's disease, while memantine is of benefit in patients with moderate to severe Alzheimer's disease**

INTRODUCTION

Dementia may be described as a clinical syndrome associated with a loss of intellectual functions including memory, significant deterioration in the ability to carry out activities of daily living (ADL) and changes in social behaviour.¹⁻⁵ Globally in 2010, it was estimated that there were 36 million people with dementia; this is expected to rise to 100 million by 2050.⁶ In 2009, it was estimated that there were 44,000 Irish people with dementia, which is expected to rise to 104,000 by 2036.^{7,8} The management of dementia is considered to be one of the greatest public health challenges facing industrialised nations for the next three decades,⁵ because of its increasing prevalence due to the ageing population, long duration, carer burden and high financial cost of care.^{1,4,5,9} Patients with dementia live 8 years on average after initial diagnosis but for as long as 20 years from the onset of symptoms.¹⁰ According to the WHO, dementia contributes to a greater percentage of years spent living with a disability in people aged >60 years, than stroke, cardiovascular disease or cancer.¹⁰⁻¹² The benefits of early assessment of dementia, when some patient insight may be retained, include identification of treatable physical and psychiatric causes of cognitive impairment (including depression, hypothyroidism and vitamin deficiencies), the treatment of co-morbid conditions, early access of patients and carers to services and initiation of pharmacological treatment when indicated.^{2,13-15} However, early recognition of dementia is not easy due to its insidious and variable onset² and confirmation of the diagnosis can take up to 4 years.¹⁶

This bulletin will provide an overview of the diagnosis and current management of dementia.

TYPES OF DEMENTIA

There are different types of dementia, the most common of which are summarised in Table 1. Dementia is often preceded by a period of mild cognitive impairment, where there are preserved ADL.^{17,18}

Table 1: Main causes of dementia

Alzheimer's Disease (AD)

- Responsible for an estimated 50% of cases of dementia.² Early onset AD which occurs at <60 years of age, accounts for up to 7% of cases and may have a significant genetic component.¹⁹ No single causal genetic mutation has been identified for late onset AD. AD is characterised by early loss of basal forebrain cholinergic neurons, leading to decreased cholinergic transmission;²⁰ the two core pathological hallmarks are amyloid plaques and neurofibrillary tangles.¹² Symptoms include memory problems, a progressive deterioration in the ability to perform basic activities of daily living, and behaviour changes including apathy and social withdrawal.^{1,2,4}

Vascular dementia (VD)

- Responsible for an estimated 25% of dementia cases in Europe;² a heterogeneous group associated with cerebrovascular damage.^{5,14,21} Onset may be abrupt or there may be periods of sudden decline followed by relative stability.^{3,14} It should be considered in people with vascular risk factors.¹⁴

Dementia with Lewy bodies

- Responsible for an estimated 15% of patients with dementia.² Lewy bodies develop in neurons in the brain leading to degeneration of nerve tissue. Characteristic features are fluctuation of awareness from day-to-day, visual hallucinations and signs of Parkinsonism such as tremor, rigidity and slowness of movement or poverty of expression.^{3,5} Dementia also occurs in up to 80% of patients with Parkinson's disease, which is diagnosed if the motor symptoms occur > 12 months before the cognitive symptoms.⁵

Fronto-temporal dementia (FTD)

- Is the second most common dementia after AD in adults <65 years of age.^{3,5} It is characterised by progressive atrophy of regions of the frontal and temporal cortex.⁵ Aetiology is unknown but there appears to be a genetic component in 40% of familial cases.^{5,22} Two broad presentations are recognised: progressive deterioration in social function and personality, known as behavioural-variant FTD and insidious decline in language skills, known as primary progressive aphasia.^{3,5,22}

Mixed dementias

- There may be two or more types of dementia in the same person. Evidence suggests that the interaction between VD and AD is complex and that rigid boundaries between the subtypes may be artificial. Response to treatments in patients with mixed dementia may be different than in those with a specific diagnosis.³

DIAGNOSIS

Most patients with symptoms of dementia present to their general practitioner (GP).¹² Diagnosis can be delayed if the patient and their family are reluctant to acknowledge the symptoms, or if there is a reluctance by healthcare professionals to consider the diagnosis.^{2,11,13,16,23} There are a number of signs and symptoms of dementia (Table 2), which may be reported by the person or family which, while not specific for dementia, may indicate that further assessment is required.²⁴

Table 2: Symptoms of dementia²⁴

Cognitive symptoms

- Memory problems including forgetfulness, repetitive questioning, difficulty finding names and not knowing common facts, disorientation
- Misunderstanding spoken and written communication

Challenging behaviours, psychiatric symptoms and personality changes

- Withdrawal or apathy, depression, agitation or anxiety
- Blunting of emotions and disinterest, social withdrawal
- Disinhibition, inappropriate friendliness, flirtatiousness
- Suspiciousness, fearfulness, aggression, psychosis (delusions, hallucinations)
- Insomnia, restlessness, wandering, agitation, noisiness

Neurological symptoms

- Gait disturbances, apraxia (loss of ability to perform learned purposeful movements)

Difficulties with activities of daily living

- Difficulty with orientation, getting lost, loss of driving skills, difficulty planning tasks
- Taking prescribed drugs erratically – for example uncharacteristic variations in INR in a person normally taking stable doses of warfarin
- Neglecting household chores, trouble with shopping, difficulty handling money, difficulty making judgements
- Neglecting hygiene or self-care, deterioration in personal appearance, or a reduction in social roles

The accurate diagnosis of dementia is a challenge for GPs and specialists²⁵ and a process that may require several consultations to gather sufficient information. There is no simple test for the diagnosis of dementia; diagnosis is made on clinical assessment and supported by results of investigations. Assessment of dementia should include a detailed history from the patient and carer, cognitive assessment, assessment of ADL, physical examination (looking for potential signs of stroke and co-morbidity) and a review of medication in order to identify and minimise use of drugs that may adversely affect cognitive functioning.^{3,4,16,17,25} While any medication may be associated with confusion particularly in a vulnerable patient (e.g. the elderly), there are some drugs which are more commonly associated with confusion (Table 3).²⁶ Treatable causes of cognitive impairment include depression, hypothyroidism and certain vitamin deficiencies.¹⁴ It is particularly **important to exclude delirium (a transient, usually reversible acute confusional state) which is a medical emergency associated with an increased risk of morbidity and death.**²⁵

Table 3: Medications associated with an increased risk of confusion²⁶.

- Hypnotics/sedatives – more common with long-acting benzodiazepines, withdrawal delirium also occurs
- Opioid analgesics – risk may be highest with pethidine
- Antipsychotics – those with considerable anticholinergic activity may worsen delirium
- Anti-parkinsonian drugs – risk is highest in those with anticholinergic activity
- Antidepressants – risk is highest with tricyclic antidepressants (TCAs)
- Anticonvulsants – all anticonvulsants can impair cognitive function
- Cardiac drugs – including digoxin (dose-related), disopyramide, calcium antagonists
- Corticosteroids – the risk is dose related

A basic dementia screen should be performed at the time of presentation and include: routine haematology, biochemistry tests (electrolytes, calcium, glucose, renal and liver function), thyroid function tests, vitamin B12 and folate levels to exclude treatable causes of impaired cognition and assess for co-morbidities.^{3,4,17} Testing for syphilis or HIV is not routinely done unless patients are considered at risk.⁴

There are a number of validated cognitive screening instruments which can be used in primary care,^{27,28} a number of which are summarised in Table 4. It is important to appreciate that performance may be affected by culture, language, hearing and educational ability. The Montreal Cognitive Assessment (MoCA) is a brief screening tool for mild cognitive impairment.^{29,30}

Cognitive screening tests are not diagnostic but they can help to decide who should be referred for specialist assessment.

Table 4: Selected cognitive screening instruments in primary care²⁷

- **Mini-Mental State Examination (MMSE)** – well established, brief (approx. 10 minutes), 30-item questionnaire sampling various cognitive domains, excellent specificity for dementia diagnosis and sensitivity less good
- **Abbreviated Mental Test Score (AMTS)** – well-established, brief (approx. 5 minutes), 10-item screen sampling various cognitive domains
- **Six Item Cognitive Impairment Test (6CIT)** – relatively new, brief (approx. 5 minutes), 9-item cognitive screening instrument sampling various cognitive domains specifically designed for use in primary care
- **General Practitioner Assessment of Cognition (GPCOG)** – relatively new, brief (approx. 5 minutes), 6-item cognitive screening instrument sampling various cognitive domains specifically designed for use in the primary care setting
- **7-Minute Screen (7-MS)** – relatively new, brief (approx. 7 minutes), battery of 4-items sampling various cognitive domains
- **Mini-Cognitive Assessment Instrument (Mini-Cog)** – relatively new, very brief (approx 3-5 minutes), screening test assessing only 2 aspects of cognition, namely short-term recall and clock drawing. Specifically designed for use in primary care
- **Memory Impairment Screen (MIS)** – relatively new, very brief (approx. 4 minutes), 4-item single domain assessment test

If assessment is suggestive of dementia the patient ideally should be referred to a specialist memory assessment service where the diagnosis of dementia can be confirmed (or ruled out), its cause established, a management plan drawn up and drug treatment started if appropriate.⁴ People whose symptoms progress rapidly or who have neurological abnormalities on examination should be referred to a neurologist. Neuroimaging including MRI or CT may be required to detect intracranial lesions or diseases that might cause (e.g. tumour, hydrocephalus) or contribute to (e.g. cerebrovascular disease) dementia syndromes.^{12,17} The accurate diagnosis of dementia subtypes has become increasingly important with the advent of licensed treatments specifically for AD, and the recognition of the potentially serious side effects of antipsychotics in people with dementia with Lewy bodies.³ A diagnosis of the subtype of dementia should be made by physicians with expertise in differential diagnosis.⁴

It is also important for patients with suspected or confirmed dementia that there is an assessment of behavioural and psychological symptoms of dementia (BPSD). This is a term used to describe the spectrum of non-cognitive symptoms of dementia (apathy, psychosis, affective and hyperactive behaviours), which occurs in the majority of patients with dementia over the course of the disease and which impacts on the management of a patient with dementia.¹⁷

NON-PHARMACOLOGICAL MANAGEMENT

The disclosure of the diagnosis of dementia is rated by primary care physicians as one of the most difficult areas in dementia management.^{16,31} An individualised approach should be taken that is sensitive to the patient's circumstances and involves the family; this may require a number of visits.³¹ Good communication between healthcare professionals, patients and carers is essential, so that people with dementia and their carers receive the information and support they require.^{3,4} While evidence suggests that lack of physical activity, midlife obesity, excess alcohol intake, smoking and head injury are important risk factors for dementia;^{17-19,32,33} there is conflicting advice as to whether lifestyle interventions of these factors are beneficial for primary prevention of dementia.^{12,17,19,34} There are many treatable medical conditions, which are also associated with an increased risk of dementia including stroke, diabetes, hypertension and hypercholesterolaemia.^{12,18}

There are a number of non-pharmacological therapies which have been shown to have a positive impact on patients with dementia including: person-centred care, cognitive stimulation, exercise, music and recreational activities.^{3,35-37} Behaviour management may be used to reduce depression in people with dementia.³

The needs of carers, many of which develop psychological problems, should be considered and should continue after the patient with dementia has entered residential care.^{4,10,38} Multidisciplinary interventions, including occupational therapy, respite care, education, counselling and support for carers, have been shown to be cost effective, to delay institutionalisation of patients with dementia and to improve the carer's health and quality of life.^{13,17,31}

PHARMACOLOGICAL MANAGEMENT

There are currently no disease modifying drugs available for the treatment of dementia. Acetylcholinesterase inhibitors (AChEIs) and memantine are authorised primarily for patients with AD.

Acetylcholinesterase inhibitors (AChEIs) – It is assumed that the mechanism of action of AChEIs relates to increased cholinergic transmission via inhibition of breakdown of acetylcholine.³ Evidence has shown that the use of AChEIs (**donepezil, rivastigmine and galantamine**) are of benefit in the management of mild to moderate AD;³⁹⁻⁴⁶ with improvements in cognition, ADL and behavioural symptoms.⁴⁰ There is insufficient evidence to differentiate between the AChEIs in terms of clinical effectiveness.^{39,46} There is some evidence suggesting that AChEIs may have a possible disease modifying effect however more data are required before this can be confirmed.^{17,40} Patients who do not tolerate one AChEI may tolerate another AChEI. The most common side effects are gastrointestinal, which occur at the start of therapy or when the dose is increased, and tend to be transient.⁴⁵ Rivastigmine administered transdermally may be associated with a lower incidence of side effects,^{17,45} and may improve compliance.⁴⁷ Evidence suggests that oral rivastigmine also improves cognition in patients with dementia with Parkinson's disease.^{48,49} There is also evidence to suggest that AChEIs may improve cognition in patients with Lewy body dementia (unauthorised indication).⁵⁰⁻⁵³

It is unclear whether AChEIs are of benefit in VD.^{40,54-57} Current guidelines recommend that they should not be prescribed for the treatment of cognitive decline in VD, except as part of properly constructed clinical studies.⁴ Patients with mixed dementia should be managed according to the condition that is thought to be the predominant cause of their dementia.⁴

Due to their pharmacological action, the concomitant use of other cholinomimetic medicinal products (e.g. neostigmine, pyridostigmine) and anticholinergics should be avoided.^{49,58-62} Prescribers should refer to the individual Summary of Product Characteristics (SmPC) for full prescribing information (including all information on drug interactions).

Memantine is a non-competitive N-methyl-D-aspartate receptor antagonist (NMDA).⁶³ The blocking of the NMDA channel modulates the effects of pathologically elevated levels of the neurotransmitter glutamate that may lead to neuronal dysfunction. Evidence supports the use of memantine in moderate to severe AD⁶³⁻⁶⁵ and a recent review concluded that memantine offered symptomatic benefits in cognitive, functional, global and behavioural outcomes in patients with moderate to severe AD, although the size of the benefit is uncertain.³⁹

There is some evidence to suggest the combination of memantine with AChEIs may be beneficial for the management of AD,^{12,63,64,66-68} however further studies are required.^{17,39,69}

Table 5 summarises the indications, common adverse effects and monthly costs of the drugs used in dementia. There are certain criteria which should be met when prescribing AChEIs and memantine; **treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of AD, they should only be started if a carer will monitor drug intake, maintenance should be continued for as long as there is a therapeutic benefit for the patient and therapy should be discontinued if therapeutic effects are no longer present.**^{49,58-62,70,71}

Table 5 Indications, common adverse effects and monthly costs of the drugs used in dementia*

Drug	Indication	Common adverse effects	Monthly costs in Euros**
Donepezil	Mild to moderate AD ⁵⁸	Nausea, vomiting, diarrhoea, headache, common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, rash, pruritus, muscle cramps, urinary incontinence, fatigue, pain	Tablet (32.71–48.60)
Galantamine	Mild to moderate AD ^{59,61}	Nausea, vomiting, diarrhoea, anorexia, hallucinations, depression, syncope, dizziness, tremor, headache, somnolence, lethargy, bradycardia, hypertension, hyperhidrosis, muscle spasms, fatigue	Tablet (44.37–109.68) Prolonged release capsule (67.65–109.68) Oral solution (100.83)#
Rivastigmine	Mild to moderate AD ^{49,62} Mild to moderate dementia in patients with Parkinson's disease ⁴⁹	Nausea, vomiting, diarrhoea, abdominal pain, anorexia, hyperhidrosis, rash, fatigue, malaise, insomnia, anxiety, restlessness, tremor, dizziness, somnolence, headache, worsening of Parkinson's disease, bradykinesia, dyskinesia, agitation, confusion, syncope, bradycardia	Capsule (66.04–73.91) Transdermal (83.31–90.27)
Memantine	Moderate-severe AD ^{70,71}	Constipation, headache, dizziness, hypertension, somnolence, dyspnoea, drug hypersensitivity	Tablet (25.14–103.68) Oral solution (92.57)#

- * Prescribers should refer to the individual summary of SmPC for full prescribing information
- ** GMS monthly costs for starting doses and the maximum recommended doses (April 2011)
- # this price represents the cost for a maintenance dose (20mg/day) of memantine and an initial maintenance dose (16mg/day) of galantamine for 25 days

Other drugs and interventions – Evidence does not support the use of statins, hormone replacement therapy, vitamin E or non-steroidal anti-inflammatory drugs for the primary prevention of dementia.⁴ Several other treatments have also been suggested as potentially beneficial for the treatment of AD including vitamin A and selegiline; however there is insufficient evidence to support the use of these agents.^{3,17,72}

There are several clinical and experimental studies ongoing for the treatment of AD, some involving agents that target mitochondrial dysfunction and amyloid function (including immunotherapeutic approaches).^{12,20}

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

It is estimated that up to 90% of patients with AD, develop behavioural and psychological symptoms of dementia (BPSD) which encompass a broad range of symptoms and signs including apathy, mood changes, agitation, aggression, delusions and hallucinations.⁷³ **BPSD are a major cause of carer distress and are associated with an earlier move to institutional care.** People with dementia who develop BPSD should be offered an assessment at an early opportunity to establish any likely factors that may generate, aggravate or improve such behaviour, including infection, pain and other co-morbidities.^{4,74,75}

Individually tailored plans that help carers address challenging behaviour should be developed and reviewed regularly.^{4,74,75} Non-pharmacological approaches including multisensory stimulation, music and/or dance therapy, animal-assisted therapy and massage have been shown to be of benefit in managing BPSD.^{4,12,35,76}

Clinicians are often under pressure to find a pharmacological solution to help distressing behavioural disturbances,⁷⁴ and evidence from the UK suggests that up to 18% of patients with dementia are prescribed antipsychotic drugs.⁷⁷ However **there is an increased risk of stroke and mortality when elderly patients with dementia are prescribed antipsychotics.**⁷⁸

Recent guidelines recommend that people with dementia with **mild to moderate non-cognitive symptoms should not be prescribed antipsychotic drugs** because of the possible increased risk of adverse events.⁴ Patients with dementia with Lewy bodies are at risk of severe adverse effects (such as neuroleptic sensitivity reactions; development or worsening of extrapyramidal features; or acute, severe physical deterioration), with use of antipsychotics.⁴

People with dementia with **severe non-cognitive symptoms** (persistent aggression, unresponsive to non-pharmacological approaches when there is a risk of harm to self or others) should only be offered short-term treatment (up to 6 weeks) with an antipsychotic drug (such as risperidone) after the risks/benefits for the individual patient are carefully assessed^{4,74,79} and fully discussed with the patient and/or carer. Specialist advice should be obtained for patients with dementia with Lewy bodies before starting an antipsychotic due to the risk of severe adverse effects.

Patients with mild, moderate or severe AD and patients with dementia with Lewy bodies with BPSD may be offered an AChEI if a non-pharmacological approach is inappropriate/ineffective and antipsychotic drugs are inappropriate/ ineffective.^{2,4,50,73,75,80}

Patients with VD who develop non-cognitive symptoms or behaviour that challenges should not be prescribed AChEI except as part of properly constructed studies.⁴

If a patient appears to be depressed the use of selective serotonin reuptake inhibitors (SSRIs) may be considered.^{74,81} SSRIs have also been used to treat disinhibition and challenging behaviours, but evidence for their use remains contradictory.²²

SUMMARY

Dementia is a progressive incurable illness, the prevalence of which is expected to rise due to the ageing population. Early diagnosis of dementia enables identification of treatable causes of dementia, the treatment of co-morbid conditions, access of patients and carers to services and initiation of pharmacological treatment when appropriate. The diagnosis and management of dementia requires multidisciplinary input and involves non-pharmacological and pharmacological approaches.

List of references available on request. Date of preparation: May 2011

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue.

Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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