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DEMENTIA

- The prevalence of dementia increases with age.
- Dementia interferes with patients' capacity to articulate symptoms and signs and can marginalise people within the healthcare system.
- Dementia management requires a multidisciplinary approach encompassing pharmacology, housing, day centres, hospital care, institutional care, psychiatric care, geriatric care and support for carers.
- Alzheimer's disease accounts for the majority of cases of dementia, although the exact subtype matters little to the patient or carer.

Dementia is an umbrella term used to describe various progressive neurological conditions affecting memory, cognition and higher executive functioning which lead to progressive impairment of activities of daily living (ADL) and a variety of behavioural and neuropsychiatric disturbances. Dementia affects 5-8% of people over age 65, 15-20% over age 75 and 25-50% over age 85.[1] Alzheimer's disease accounts for up to 75% of cases of dementia. While over 35,000 people have a diagnosis of dementia in Ireland[2], a diagnosis of dementia creates significant stress and morbidity for carers and therefore affects a far greater number.

DIAGNOSIS

The diagnosis of dementia can only be made when delirium has been excluded. **Essential features of dementia** are *memory impairment* plus one of the following: *aphasia* (loss of articulation, comprehension of written / spoken word), *apraxia* (loss of coordination of movements / manipulation of objects), *agnosia* (loss of ability to interpret sensory stimuli) or a *disturbance in higher executive functioning* (abstract thinking, ability to perform complex multitask functions – planning, initiating, sequencing, monitoring or ending a complex task).[3] There is not a direct relationship between the functional and cognitive decline and they may proceed at different paces. These features impact significantly on a patient's social and occupational level of functioning. **Associated non-cognitive** or **neuropsychiatric symptoms** include behavioural disturbances (irritability / agitation / aggression / wandering), delusions, hallucinations, anxiety and depression. These occur in up to 60-98% of patients with dementia, particularly in advanced stages, and are associated with significant caregiver stress and depression.[3] A diagnosis of dementia requires an accurate history (including a collateral history) and detailed cognitive, behavioural and functional assessments. Once cognitive decline is established and delirium is excluded, potential causes and co-morbidities should be screened for. **The principal differential diagnoses** are 1) delirium (abrupt onset, fluctuation in the level of cognitive deficits), 2) depression (pseudodementia), 3) schizophrenia (background of psychotic behaviour, associated with less severe cognitive impairment), 4) hypothyroidism, 5) normal pressure hydrocephalus, 6) vitamin B12 deficiency and 7) amnesic disorder (memory impairment but no cognitive deficits).

DEMENTIA SUBTYPES

Alzheimer's disease (AD) is characterised by the progressive loss of cognitive abilities, memory and functional autonomy and the development of neuropsychiatric problems and behavioural disturbances. A German neurologist Alois Alzheimer first described the condition in 1907. Excess production and accumulation of beta-amyloid (Aß) peptide are thought to be responsible for AD.[3] Other hypotheses include tau-protein abnormalities, heavy metal exposure, vascular factors and viral infections. Definitive diagnosis is only possible at autopsy with documentation of senile plaques and neurofibrillary tangles in the cerebral cortex. A clinical diagnosis correlates with a pathological diagnosis in 70 – 90% of cases. Known associated risk factors include: advanced age (1% of 60-year-olds and about 30% of 85-year-olds are affected), presence of ApoE4 gene, cigarette smoking, family history and gender (more females are affected).[4] AD has an insidious onset, typically between the sixth and eight decade, and is associated with a gradual but relentless decline. **Ten warning signs of AD** are memory loss affecting job skills, difficulty performing familiar tasks, problems with language, disorientation to time and place, poor or decreased judgment, problems with abstract thinking, misplacing things, changes in mood or behaviour, changes in personality and loss of initiative.[5]

Vascular dementia (VaD) accounts for 20% of dementia. Risk factors include: cerebrovascular pathology (probability of dementia one year post stroke is 5.4% in persons > 60 years and 10.4% in persons > 90 years), midlife hypertension, cigarette smoking and diabetes mellitus.[6] It may be associated with features of AD (**mixed dementia**).

Up to 60-80% of patients with long-term **Parkinson's disease** develop dementia. It is characterised by cognitive and memory impairment as well as motor slowing.[7,8]

Dementia with Lewy bodies accounts for 7-26% of dementia cases and is associated with prominent visual hallucinations and parkinsonian features and a more rapid clinical course.[6,9]

CLINICAL COURSE & PROGNOSIS

Dementia is a progressive disorder. Patients with **mild dementia** tend to have difficulties carrying out complex tasks, repeat themselves, and their forgetfulness interferes with ADL. This phase may last 2 to 4 years. Patients with **moderate dementia** tend to have difficulty with housework, require reminders about their personal hygiene, get lost easily, experience restlessness and agitation, have difficulty sleeping and may have delusions. This phase may last 2 to 10 years. Patients with **severe dementia** may not be able to use or understand words, recognise family members, move around independently and require assistance with all their daily activities. This phase may last 1 to 3 years. In **profound dementia**, patients are largely oblivious to their surroundings and are totally dependent for all care. Potential terminal complications include septicaemia, pneumonia, upper respiratory tract infections, nutritional disorders, pressure sores, fractures and wounds.

Dementia shortens life expectancy, though actual survival estimates vary. A Canadian Study of Health and Aging found the adjusted median survival from time of diagnosis for those with probable AD and VaD was 3.1 and 3.5 years respectively.[10] Another US study found the estimated median survival from dementia onset to death was 3.9 years for those with VaD, 7.1 years for AD and 5.4 years for mixed dementia.[11]

MANAGEMENT OF DEMENTIA

Guidelines for the diagnosis and management of AD are available.[1,5] A definitive diagnosis of dementia is the first step in management. The nonpharmacological and pharmacological management of the amnesic elements and the neuropsychiatric symptoms are discussed below.

NONPHARMACOLOGICAL MANAGEMENT

There is an evolving concept of the "at risk brain" with parallel development of "brain protection strategies" – wearing seat belts, avoiding boxing, caring for one's arteries (blood pressure, lipids etc.).[12] For patients with dementia, general health maintenance activities such as - exercise, control of hypertension, influenza vaccination, dental hygiene and assessment of eyeglass wear and hearing aids should be encouraged.[13] The following improve functional performance: low lighting levels, music and simulated nature sounds (beneficial particularly at meal and bathing times), graded assistance, positive reinforcement and intensive multi-modality group training.[1,3]

Specific areas of concern for patients with **mild to moderate dementia** are driving, cooking, and wandering. Forgetfulness, poor insight and judgement, easy distractibility, and problems following directions add to the difficulties for patients and their carers. Six-monthly review of dementia severity and appropriateness of continued driving should be performed. The risk of driving-related-accidents is the same in the first year after diagnosis as for drivers of all ages, but increases significantly thereafter.[12,14]

Areas of concern for those with **severe dementia** are urinary incontinence, falls and aggressive behaviour. Urinary incontinence may be reduced by behaviour modification, scheduled toileting and prompted voiding.

PHARMACOLOGICIAL MANAGEMENT

A definitive diagnosis by a specialist in this area is recommended before commencing drug therapy. Commonly used scales in clinical trials to assess dementia severity include the Clinician's Interview-Based Impression of Change with Caregiver input (CIBIC-plus), the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and the more widely used Mini Mental State Examination (MMSE).[3] In untreated patients, the ADAS-Cog has a typical rate of increase (reflecting clinical deterioration) of 7 points a year.[3] In clinical trials, a 4-point decrease is equivalent to reversing the symptoms of the disease by approximately six months, and a 7-point decrease is equivalent to a one-year reversal.[3]

Cholinesterase inhibitors: Cerebral production of choline acetyl transferase is reduced in dementia, resulting in impaired cholinergic function. Cholinesterase inhibitors (CIs) inhibit cholinesterase at the synaptic cleft and increase cholinergic transmission. Three CIs are licensed in Ireland for the treatment of mild to moderate AD: donepezil (*Aricept*®), rivastigmine (*Exelon*®) and galantamine (*Reminyl*®).

Efficacy: Clinical trials of CIs[15-17] have shown changes of 2.5-3.5 points on the ADAS-Cog and differences of 0.3-0.5 on the CIBIC-Plus. Three times as many patients receiving a CI had a 7-point improvement on the ADAS-Cog versus placebo and approximately twice as many patients who received a CI had a 4-point improvement on the ADAS-Cog versus placebo.[3,18] Positive secondary endpoints in the

CI - placebo controlled clinical trials included helping affected patients maintain their ability to perform ADL, development of fewer behavioural changes, being less of a burden to their caregivers and deferral of nursing home placement. A meta-analysis of 29 randomised placebo-controlled trials of CIs demonstrated that CI use was equivalent to preventing a two months per year decline in a typical patient with AD.[19] Studies of greater than one year duration of CI use have shown continued benefits.[21, 22] A NICE guidance in 2001, recommended that the three CIs be used in the treatment of mild to moderate AD. The Appraisal Committee of NICE (March 2005) currently advises that there is a gain on cognitive and global scales associated with CI use but that CI use is not cost effective within the NHS – full guidance and final opinion is expected in October 2005.[24] It is unclear if patients with moderate to severe dementia benefit from CI therapy. Initial dosing, recommended maximum dosing schedules and monthly cost of the products are outlined in Table 1.

Safety: Side effects include nausea (17-37%), vomiting (10-21%), diarrhoea (12-19%), and less commonly: insomnia, weight loss, abnormal dreams, muscle cramps, bradycardia, syncope and fatigue. The frequency and severity of side effects lessens with slower rates of drug titration and is generally lower with maintenance therapy.

Summary & Practical Advice: CIs slow cognitive decline and functional deterioration temporarily and may reduce the emergence of new behavioural disturbances, but they do not affect the underlying disease process. Benefits in cognitive function have been demonstrated in mild to moderate AD, VaD and dementia due to Lewy bodies (the latter two are unlicensed indications at present). CIs should be introduced at low doses and the dose should be increased gradually (4 - 6 week intervals). The optimal time to commence these drugs, optimal duration of use and CI of choice is unclear at the present time.

Memantine (*Ebixa*®) a N-methyl-D-aspartate (NMDA) antagonist is licensed in Ireland for the treatment of moderate to severe AD. Patients with AD are known to have excessive activation of NMDA receptors leading to neuronal damage and death (excitotoxicity). Memantine binds to NMDA receptors and inhibits excitotoxicity, and thus appears to be neuroprotective.

Efficacy: A placebo controlled study found memantine significantly reduced deterioration on two scales of clinical efficacy.[25] A placebo controlled study of the addition of memantine to stable doses of donepezil therapy in patients with moderate to severe AD found the combination resulted in significantly better outcomes in measures of cognition, ADL and behaviour.[26] A Cochrane Database review found memantine was well tolerated and associated with a clinically noticeable reduction in functional and cognitive deterioration over 28 weeks in patients with moderate to severe AD.[27] The effect of memantine in mild to moderate AD is unknown at present. The preliminary consultation document from the Appraisal Committee of NICE (March 2005) states that memantine has beneficial effects - in terms of functional, cognitive and global measurements - in moderately severe to severe AD. The Committee however conclude that it is not recommended for therapy in moderately severe to severe AD within the NHS (full guidance and final opinion expected October 2005).[24] Small statistical improvements in ADAS-cog scores in two placebo-controlled trials of patients with mild to moderate VaD have been found with memantine use.[28]

Safety: While the incidence of side effects is low, those noted with use include hallucinations, dizziness, confusion, headache and fatigue.

Vitamin E and **Selegiline**: A placebo-controlled study compared the effect of Vitamin E, selegiline, their use in combination or placebo in patients with AD. A significant benefit in the primary outcomes (time to death, nursing home placement, development of severe dementia), was found with the three active therapy arms but there was no significant difference in cognitive function between the four arms of the study.[29] Cochrane reviews have found that there is insufficient evidence of efficacy associated with Vitamin E or selegiline to justify their use .[30,31]

Ginkgo biloba has been shown to have small statistically significant beneficial effects in placebo-controlled studies of patients with AD. A systematic review of 33 trials of ginkgo use in dementia concluded that while it appears to be safe, it is of questionable efficacy and due to lack of regulation - with variability in the dosing and contents of herbal medicines - its use is not advocated.[32]

Theoretical reasons exist for beneficial effects of **oestrogens** (hormone replacement therapy) and epidemiological data suggest **NSAID** use may be associated with a lower incidence of dementia, but at present there is no evidence that either are effective as therapy.[33-37]

NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA

Neuropsychiatric symptoms of dementia (NPSD) include abnormalities of perception, thought, mood and behaviour. Behavioural problems include wandering, repetitive behaviours, pacing, physical aggression and vocalisations including cursing and screaming. Aggression, agitation, hallucinations and depression are the principal NPSD that lead to nursing home placement.[24]

Nonpharmacological Management:

Problem behaviours such as wandering, hoarding, repetitive questioning and social inappropriateness may respond to behavioural therapies.[28] Other therapies of benefit include: aromatherapy, reality orientation, validation therapy, reminiscence therapy, art, music, activity therapy, bright-light therapy and multi-sensory stimulation.[1,3,40]

Pharmacological Management:

Delusions, hallucinations and aggressive behaviour may be short-lived and unobtrusive or debilitating and severe. Acute onset of these symptoms warrants investigation to outrule acute delirium as a result of infection, sleep disturbance, or a recent medication change. Use of cholinesterase inhibitors and/or memantine is associated with a modest improvement in the NPSD associated with dementia.[19,20,41] A review of pharmacological therapy of NPSD found no clear evidence that the typical antipsychotics (thioridazine, chlorpromazine, haloperidol) were associated with benefit and that adverse effects (sedation, extrapyramidal effects) were common.[41] The review found that the atypical antipsychotics risperidone (*Risperdal*®) and olanzapine (*Zyprexa*®) had greater evidence of efficacy, although a previous systematic review found that the evidence to support the perception of improved efficacy and adverse event rates was limited.[41,42] *Readers are reminded* that the use of these atypical antipsychotic agents in patients with dementia has been found to be associated with a 2-3 fold increase in cerebrovascular adverse events (CVAE): risperidone versus placebo 3.3% versus 1.2% (33/989 patients versus 8/693 patients); olanzapine versus placebo: CVAE 1.3% versus 0.4%, death 3.5% versus 1.5%.[43,44]

Other agents that have been tried for agitation in dementia include antiepileptics, buspirone and benzodiazepines. Their use is limited by the lack of efficacy data and their side effect profiles.[1]

Summary & Practical Advice: Appropriate first line approaches for mild NPSD include environmental manipulation or behavioural therapies. When medication is required (severe symptoms / psychosis / carers unable to cope with serious behaviour problems) – a "3T" approach is good practice: a) drug treatments should have a specific **target symptom**, b) the starting dose should be low and **titrated** upwards and c) drug treatments should be **time limited**. The decision to commence and continue an atypical antipsychotic is best taken on a case-by-case basis on the balance of potential risks (CVAE) and benefits (improving symptom).[45] Risperidone is licensed in Ireland (olanzapine is not) for use with caution for the treatment of severe behavioural disturbances in patients with dementia.[44]

Depression is a difficult diagnosis to make in a patient with impaired cognition. Depression in the elderly may present with evidence of cognitive impairment, a phenomenon called "depressive pseudodementia". Elderly patients with depression are at increased risk of developing dementia.[46] In difficult cases, a therapeutic trial of antidepressant medication is a reasonable therapeutic strategy, although there are few studies to guide selection of antidepressants in this setting. Tricyclic antidepressants may cause worsening confusion. Studies of SSRIs - citalopram (*Cipramil*®) and sertraline (*Lustral*®) have shown superiority over placebo in reducing depression symptoms in the setting of dementia.[47,48]

Sleep disturbances are common in all stages of dementia. An activity programme, avoiding daytime naps, elimination of evening alcohol and caffeine, and having a sleep routine are of benefit. Pharmacological therapy may be necessary.

CAREGIVERS

In the UK, it is estimated that 22% of people with dementia live alone, 36% with carers and 29% in nursing homes.[24] Studies show that caregivers rate their own health as poor, they have a greater number of illnesses, somatic symptoms, depression and anxiety, and engage in fewer preventative-health activities. The rate of assault on staff in nursing homes is high, in one study 60% of staff and carers reported at least one weekly assault and 16% reported daily assaults.[49] Self-help groups, support groups, education, skills training, counselling and psychotherapy have been shown to reduce psychological distress and improve caregivers knowledge, but have failed to reduce their burden.[3,50] The Alzheimer Society of Ireland provide useful and up-to-date literature and support and also operate a national helpline (www.alzheimer.ie).

SUMMARY

Dementia is a progressive incurable illness. Current therapies ease symptoms by providing temporary improvement and reduce the rate of cognitive decline. Important points to remember are a) all confused patients do not have dementia, b) delirium should always be excluded prior to a diagnosis of dementia and c) pharmacology plays a small part - and may not be necessary for all patients - in the management and support of a patient with dementia. Given the increasing incidence and the burden of care associated with this illness, the development of interventions that delay the onset or modify the progression of dementia are crucial for the patients, their caregivers and the healthcare system.

Table 1. Cholinesterase inhibitors and memantine use in Dementia[57, 58]

DRUG	CLASS*	INDICATION	DOSAGE	COST**
Donepezil (*Aricept*®)	CI	Mild-moderate AD	5mg/day - Max 10mg/day	95.08 – 133.26
Rivastigmine (*Exelon*®)	CI	Mild-moderate AD	1.5mg bd - Max 6mg bd	85.47 – 87.84
Galantamine (*Reminyl*®)	CI	Mild-moderate AD	4mg bd - Max12mg bd	76.44 – 117.32
Memantine (*Ebixa*®)	NMDA	Moderate-severe AD	5mg/day - Max 10mg bd	59.29 – 118.59

*CI = Cholinesterase inhibitor, NMDA = N-methyl-D-aspartate antagonist

** Costs: GMS monthly euro costs for starting doses and the maximum recommended doses (March 2005)

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