Alzheimer's disease: updated guidance from NICE

There has been considerable controversy over several years regarding the use of cholinesterase inhibitors and memantine for the treatment of Alzheimer's disease. In a recently published technology appraisal, NICE has reversed previous guidance on the use of these drugs in England and Wales. In this article, aspects of the diagnosis and management of Alzheimer's disease in the light of this guidance are reviewed.

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Dementia causes more morbidity, in terms of years lived with disability in people aged over 60 years, than stroke, cardiovascular disease or cancer.[1] It costs more to the UK economy (£27,647 per person each year) than cancer and cardio- and cerebrovascular disease combined (£14,224 per person per year), with a total cost of over £23 billion.[2] With the ageing population, dementia prevalence will more than double over the next four decades causing significant additional burden to patients, carers and the health and social care systems.[3]

Dementia is a complex, chronic, progressive clinical syndrome of higher cortical dysfunction, characterised by deficits in memory, thinking, orientation and comprehension, calculation, learning capacity, language and judgement. Alzheimer's disease (AD) is the leading cause of dementia.

The hallmark neuropathological features are extracellular amyloid plaques and intracellular neurofibrillary tangles, with synaptic loss and neuronal cell death, which probably develop insidiously over many years, perhaps decades, before symptoms develop and the person presents to their doctor.

Although improving in recent times, key issues for clinicians remain recognition, particularly in mild disease, and the importance of early diagnosis.[4,5] Currently, treatment is symptomatic, not curative. Management of the behavioural and psychological symptoms of dementia (BPSD) is challenging. This article will highlight the recent updated appraisal from NICE on treatment for AD.[6]

Diagnosis

Currently, the diagnosis of AD remains a clinical one, although work proceeds apace in developing reliable and robust biomarkers in blood, cerebrospinal fluid and neuroimaging. A subjective complaint of memory impairment should lead to a more detailed enquiry, preferably corroborated by an informant; physical examination, specifically with attention to the cardiovascular and neurological systems; a brief global, screening neuropsychological test; and, routine laboratory evaluation, including blood count, biochemistry panel, thyroid function and vitamin B12 and folate. Neuroimaging is recommended.[4] Screening memory tests suitable for use in primary care include the Folstein Mini Mental State Examination (MMSE), General Practitioner assessment of Cognition (GPCog), Six Item Cognitive Impairment Test (6CIT) and Montreal Cognitive Assessment (MOCA). Discussion of the relative merits of these instruments is beyond the scope of this article.

Referral to specialist memory services in secondary care is recommended to establish the diagnosis; provide information, counselling and support to patients and carers; institute treatment, regularly review response and check for adverse

drug effects; identify and manage complications, comorbidity and polypharmacy; assess for emerging BPSD; and, coordinate input from members of the specialist service, such as geriatricians, old age psychiatrists, psychologists, occupational therapists, nurse and speech and language therapists, as well as social care and the voluntary sector.[4] Good communication between primary and secondary care is vital and shared care protocols helpful.

Management

Alzheimer's disease remains a progressive, incurable neurodegenerative condition that robs sufferers of their most human of features, ends in premature death and generates considerable emotional and financial burden on carers. Currently available pharmacological treatment is symptomatic only. However, management encompasses much more than the medications that have long been under scrutiny through previous[7] and more recent assessments by NICE.[6]

Non-pharmacological management

Discussion of the diagnosis with the patient and caregiver, particularly in milder stages of the disease where the patient retains insight, relieves patient anxiety and caregiver stress, improves quality of life and allows future legal, financial and care arrangements to be planned.[4,8]

Exercise training benefits fitness, physical function, cognitive and behavioural symptoms in patients and, combined with behavioural management training for caregivers, improves physical health and mood.[9,10] Cognitive training or rehabilitation, particularly in patients taking cholinesterase inhibitors, has benefits in cognition, mood and behaviour.[11] An occupational therapist delivered cognitive training programme for patients and behavioural interventions for carers improves patient function, relieves caregiver stress, improves quality of life and health status of both patient and caregiver and is cost-effective.[12, 13]

Early involvement of community support services, for example home nursing and personal care, meals-on-wheels provision, respite care and sitting services, and day centre attendance, reduces institutionalisation, but despite significant burden and poor quality of life caregivers do not avail of these services.[14] This may be due to denial of need, lack of awareness of services, fear of invasion of privacy or refusal by the patient and lack of availability of appropriate services. This is an important area, which must be targeted and resourced by primary care services and commissioners. The needs of patients and caregivers change over time as the disease progresses and function declines. Reassessment at regular intervals is crucial.

Interventions for caregivers improve their physical and mental health and, as a result, delay the institutionalisation of the patient with AD.[15,16] Counselling sessions, regular support group meetings and availability of emergency telephone support are effective.

Although early intervention for intercurrent illness may ameliorate the excess morbidity and mortality experienced by AD patients, palliative care needs at the end-stage are unmet.[17] End of life care, particularly in nursing homes, is often inadequate with pain poorly recognised and undertreated.[18]

However, the availability of non-pharmacological interventions is variable across the UK and dependent on social care budgets. Few patients and caregivers will be offered this broad range of effective therapies.

Pharmacological management

Currently available licensed pharmacological therapies for the management of AD are the cholinesterase inhibitors donepezil (Aricept), galantamine (Reminyl) and rivastigmine (Exelon) and the NMDA receptor antagonist memantine (Ebixa). Previous guidance from NICE restricted the use of these agents in England and Wales.[4,7] Cholinesterase inhibitors were recommended as options for the management of AD of moderate severity only. Memantine was not recommended as a treatment option except as part of well-designed clinical trials. Moderately severe AD was defined as an MMSE of between 10 and 20 points. Exceptions were specified for scores outside these boundaries if moderate dementia was judged on the basis of functional impairment, in people with learning disabilities and in people not fluent in spoken English.

Although classification of disease severity as mild, moderate or severe can be helpful from a clinical and prognostic aspect, it is by its very nature arbitrary. NICE previously recommended classification based on cognition only using a global screening instrument,

the MMSE. A useful tool, the MMSE has acknowledged limitations. Specialists generally determine severity through functional, behavioural and global assessments, as well as cognitive deficits.

European and North American practice guidelines have long recommended cholinesterase inhibitor use as soon as the diagnosis of AD is established.[19-21] Available evidence suggests that the effects of cholinesterase inhibitors are similar at all stages of AD severity and that delayed initiation of treatment is detrimental. The efficacy of the three cholinesterase inhibitors is similar and improvement in measures of cognition, function and behaviour are observed.[22] Importantly, delay in the emergence and modulation of BPSD is noted.[23] Cholinesterase inhibitor treatment delays institutionalisation and reduces caregiver distress and burden and time providing care.[24]

Cholinesterase inhibitors are well tolerated and relatively safe. Contraindications include the presence of significant electrocardiographic abnormalities, peptic ulcer disease and severe chronic obstructive pulmonary disease. Adverse events are more common at the initiation of treatment and on dose titration, are mostly gastrointestinal and often responsive to symptomatic treatment. Rarely symptomatic bradycardia and syncope occur, but ChEI treatment can often be restarted.[25]

Previous NICE guidance was that cholinesterase inhibitor treatment should only be continued whilst the MMSE was 10 or greater and was considered to be having a worthwhile effect.[4,7] Effectiveness does decline during the course of cholinesterase inhibitor treatment and should be discussed with patients and caregivers. However, withdrawal of cholinesterase inhibitors can lead to recurrence of symptoms, loss of cognitive gains and a rebound increase in BPSD, indicating that the medication was still having a clinical effect.[26] If withdrawal is indicated, the patient, caregivers and primary care practitioner must be made aware of these outcomes and that medication may need to be quickly reintroduced.

Memantine acts on the glutamatergic system to reduce excitotoxicity. A Cochrane review noted benefit on cognitive and functional outcomes and that memantine was well tolerated, with the overall incidence of adverse effects no different from placebo.[27]

In a recent Final Appraisal Determination, NICE has updated previous guidance and now recommends that the three cholinesterase inhibitors donepezil, galantamine and rivastigmine are options for managing mild to moderate AD and that memantine is an option for managing AD for people with moderate AD who are intolerant of or have a contraindication to cholinesterase inhibitor or people with severe AD.[6] Treatment should only be initiated by clinicians experienced in the management of people with dementia, continued only whilst it is considered to have worthwhile effects on cognitive, functional, behavioural and global symptoms and reviewed regularly using cognitive, functional, behavioural and global assessments. Review should be undertaken by an appropriate specialist team, unless locally agreed protocols for shared care are in place. Caregivers' views on the patient's condition at baseline and on follow-up should be sought.

Management of behavioural and psychological symptoms

These disturbing symptoms, such as agitation, aggression, wandering, depression, apathy, hallucinations and sleep disturbance, are prevalent across the disease course, persistent, occur in clusters, increase caregiver burden and distress and commonly precipitate institutionalisation.[28] Antipsychotic medications are widely used off-license as treatments for BPSD, despite limited evidence for efficacy and significant evidence of increased cerebrovascular morbidity and overall mortality.[28] Risperidone is licensed for the treatment of persistent aggression in people with moderate to severe AD for up to six weeks. Currently, there is considerable political impetus for substantial reduction in the unacceptable levels of antipsychotic prescribing in people with AD.[28]

Non-pharmacological options for management of BPSD include reality orientation, validation therapy, reminiscence therapy, structured activity, environmental manipulation and bright light therapy, amongst a myriad of proposed treatments.[28] Evidence of efficacy is mostly equivocal.[29]

Cholinesterase inhibitors are associated with improvements in mood, apathy and aberrant motor behaviour, primarily in mild to moderate AD, and delay emergence of BPSD if initiated early.[29] As previously noted, withdrawal of cholinesterase inhibitors can lead to behavioural deterioration. NICE concluded that ChEI may offer some benefit in behavioural outcomes, although the nature and extent are uncertain.[6]

Memantine can be effective for the treatment of agitation/aggression and psychosis in AD.[30] The NICE committee stated that memantine may be considered as an alternative to antipsychotics for people with severe AD who have behavioural symptoms requiring treatment.[6]

Conclusion

Dementia and Alzheimer's disease have rightly been considered a national priority by recent UK governments and by the devolved administrations. Significant work remains to implement the numerous policy documents, strategies and guidance published in recent years. Not to do so will result in failure to provide optimal care for some of the most vulnerable members of our society, failure to assist caregivers and relieve their significant burden and failure in containing the burgeoning costs to the NHS and economy.

Dr Todd has received honoraria and expenses from the manufacturers of cholinesterase inhibitors. Professor Passmore has received honoraria, expenses and research funding from the manufacturers of cholinesterase inhibitors and memantine.

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