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UPDATE ON THE MANAGEMENT OF DEMENTIA

- **The prevalence of dementia is increasing**
- **Timely diagnosis allows for optimal management of dementia and enables the patient and carer to plan for the future and access the appropriate support organisations**
- **Individual dose titration of cholinesterase inhibitors is recommended; adverse effects may be reduced by increasing the dose slowly**
- **Antipsychotics for behavioural and psychological symptoms of dementia should only be prescribed if non-pharmacological approaches have failed and antipsychotics are considered absolutely necessary**

INTRODUCTION

Dementia is a disorder, characterised by progressive cognitive impairment that is associated with impairment in functional abilities and in many cases behavioural and psychological symptoms.[1,2] **Dementia is a major cause of disability and dependency.**[3] The global prevalence of dementia is rising, primarily due to an ageing population,[4] although the incidence appears to be decreasing in some countries (e.g. US and UK).[4-8] In Ireland, figures from 2016 estimated that there were >55,000 people with dementia; this number is predicted to increase to >157,000 in 2046.[9] Dementia usually presents in older age, with an exponential increase in incidence with age ≥65 years; overall approximately 80% of people with dementia are aged ≥75 years.[4] **Dementia has a major impact on patients and their families with significant societal and financial implications.**[1,4,5] Irish figures from 2010, estimated that the costs related to dementia were >€1.69 billion, approximately half of which was attributable to care provided by family/carers.[10] Under-diagnosis of dementia is common; up to 50% of patients are undiagnosed or unaware that they have dementia.[11-13] Many countries have developed national strategies on dementia, where **there is an increasing focus on risk reduction, timely diagnosis and early intervention;**[1-5,14] Ireland's National Dementia Strategy was published in 2014.[2] This bulletin will outline the current management of dementia.

RISK FACTORS FOR DEMENTIA

There are many risk factors for dementia, of which age is the strongest; other non-modifiable risk factors include gender and genetics.[2,4] Mild cognitive impairment (MCI), which usually precedes dementia, is also a risk factor; dementia differs from MCI, in that the cognitive decline seen in dementia affects activities of daily living (ADL) or social functioning.[1,4,15,16] Studies have identified nine potentially modifiable risk factors for dementia, which are summarised in table 1.[4]

Table 1: Potentially modifiable risk factors for dementia[4,17-24]

Risk factor	RR for dementia	Effects
Early life (age <18 years)		
Less education	1.6	A low educational level is thought to result in vulnerability to cognitive decline due to less cognitive reserve. Cognitive resilience in later life can be enhanced by building brain reserve earlier in life through education and with complex patterns of mental activity in later life
Midlife (45 to 65 years)		
Hypertension	1.6	Evidence suggests that control of hypertension is protective for MCI
Obesity	1.6	Obesity has been associated with increased risk of dementia
Hearing loss	1.9	Hearing loss occurs in 32% of people ≥55 years. Studies have shown that even mild levels of hearing loss increase the long-term risk of cognitive decline and dementia
Later life (>65 years)		
Smoking	1.6	Association with dementia might be due to link between smoking and CVD, but cigarette smoke also contains neurotoxins
Depression	1.9	Studies have found a link between depression and dementia
Physical inactivity	1.4	Older adults who exercise are more likely to maintain cognition than those who do not exercise. Exercise is also beneficial in older people without dementia e.g. improves balance and reduces falls, improves mood and reduces mortality
Social isolation	1.6	This may be a prodromal symptom for dementia however increasing evidence suggests it is an independent risk factor
Diabetes	1.5	The association with dementia is present for vascular dementia and Alzheimer's disease

RR-relative risk; MCI–mild cognitive impairment; CVD-cardiovascular disease

Prevention of dementia: Disease modifying drug treatments are not currently available for dementia however, **intensive risk factor modification may potentially delay or prevent dementia.**[2,4] The decline in the prevalence of dementia in some countries is thought to be associated with an increase in education and improved lifestyle factors.[4,6-8] **Multi-modal interventions incorporating diet, exercise, cognitive training and vascular risk monitoring, have been shown to maintain or prevent decline in cognitive function, among older at-risk individuals.**[25,26] Studies suggest that delaying the onset of dementia by 5 years, could half the prevalence rates; this would benefit even the oldest adults.[2,4] Areas to consider targeting to prevent or delay dementia include: 1) lifestyle (e.g. increased physical activity, healthy diet and avoid smoking), 2) medical co-morbidities (e.g. identify and treat vascular risk factors and assess hearing) and 3) mental and social well-being.[4,18,27,28] Studies from several countries including Ireland report that many people are unaware of these potentially modifiable risk factors; therefore public awareness and education campaigns are needed.[2,4,29,30] **Pharmacological interventions, including non-steroidal anti-inflammatory drugs, statins, vitamins and ginkgo biloba, have not been shown to prevent dementia.**[4,26,31-33]

TYPES OF DEMENTIA

Dementia is an umbrella term that refers to a syndrome characterised by a progressive decline in cognitive function.[1] There are many different types of dementia, the most common are Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) (see table 2); mixed dementia with more than one sub-type is also common.[4] Other types of dementia include alcohol-related dementia and HIV-dementia.

Table 2: Most common types of dementia[1,15,34-41]

Type of dementia	Main characteristics
Alzheimer's disease (AD)	Occurs in approx. 60 to 80% of patients with dementia. Insidious and irreversible memory decline is the most recognised feature, beginning with short-term deficits but other areas of cognition such as word-finding, visuoconstructional and executive abilities can also decline
Vascular dementia (VaD)	Causes or contributes to 25 to 50% of patients with dementia. Due to cardiovascular or cerebrovascular disease; may occur following stroke. Progressive or stepwise cognitive decline and prominent impairment of executive function
Dementia with Lewy bodies (DLB)	Occurs in approx. 15% of patients with dementia. Progressive cognitive decline accompanied by core features: visual hallucinations, fluctuating attention and cognition and motor features of parkinsonism. Up to 40% of patients with Parkinson's disease (PD) develop PD dementia (PDD). The main clinical distinction between DLB and PDD is temporal; in DLB the dementia presents before the parkinson symptoms, while in PDD, the dementia symptoms develop after the patient has PD for many years
Frontotemporal dementia (FTD)	Most common early-onset dementia; onset usually in the 6th decade of life. Substantial genetic component. Group of heterogenous disorders characterised by prominent changes in social behaviour and personality or aphasia associated with progressive atrophy of the frontal and/or temporal lobes. May develop a concomitant motor syndrome such as parkinsonism

DIAGNOSIS OF DEMENTIA

Early diagnosis of dementia enables the patient to plan for the future, benefit from treatment and access support organisations.[1,4,5] **The diagnosis of dementia can be challenging due to its insidious onset and variability of presenting symptoms**; a definitive diagnosis may require several consultations and take up to 20 months from first symptom recognition.[1,5,42] The GP is often the first healthcare professional (HCP) to be consulted when dementia is suspected;[1,5] on average, GPs will have 12 to 15 patients with dementia, and diagnose approximately 2 patients with dementia each year.[1,43,44] The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for diagnosis of dementia are listed in table 3.

Table 3: Criteria for diagnosis of dementia (DSM-5)[45]

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains:
   - Learning and memory
   - Language
   - Executive function
   - Complex attention
   - Perceptual-motor
   - Social cognition

B. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications

C. The cognitive deficits do not occur exclusively in the context of a delirium

D. The cognitive deficits are not better explained by another mental disorder (e.g. major depressive disorder, schizophrenia)

Assessment of a patient with suspected dementia requires: 1) a history from the patient and a relative/carer (e.g. pattern of cognitive impairment and impact on ADL), 2) physical examination including neurological, visual and hearing assessment, 3) medication review, 4) cognitive assessment and 5) investigations (see table 4).[1,3,4,16,34,46] **It is important to identify co-morbid conditions and potentially reversible causes of cognitive decline e.g. depression, delirium, drugs, vitamin B12 deficiency and thyroid disturbance.**[1,3-5] Many validated cognitive tests are available, of which the most widely used is the MMSE;[1,4,46-48] the GPCOG, MIS and MINI-Cog are also appropriate for use in primary care (table 4).[49-51] **Performance may be affected by culture, language, hearing, visual and educational ability.**[1,4]

Table 4: Assessment of dementia in primary care[1,5,34,44,46,49-51]

Blood tests
- Full blood count, thyroid function, renal and liver function, calcium, glucose and vitamin B12 *

General medical investigations
- Chest X-ray and MSU if clinically indicated and ECG (as ChEIs may induce sinus bradycardia)

Cognitive assessment tools used in primary care include: **
- Mini-Mental State Examination (MMSE)
  - approx. 10 minutes to administer, 30-item questionnaire sampling various cognitive domains. Educational and cultural bias. (sensitivity 69-91%; specificity 87-99%). Copyright restrictions
- General Practitioner Assessment of Cognition (GPCOG)***
  - approx. 5 minutes to administer, 6-item cognitive assessment with the patient and an informant questionnaire. Free of educational bias (sensitivity 82-85%, specificity 83-86%)
- Mini-Cognitive Assessment Instrument (Mini-Cog)***
  - approx. 3-5 minutes to administer, assesses 2 aspects of cognition, namely short-term recall and clock drawing. Free of educational bias. (sensitivity 76-99%, specificity 89-93%)
- Memory Impairment Screen (MIS)***
  - approx. 4 minutes to administer, 4-item delayed recall and cued recall. Free of educational and language bias (sensitivity 74-86%, specificity 89-96%)

*Additional tests such as syphilis and HIV serology should be considered in patients at risk or with clinical features; ** additional short cognitive tests used in primary care include abbreviated mental test score (MTS) and six item cognitive impairment tool (6CIT); *** accessible at www.dementiapathways.ie

MSU-midstream specimen of urine; ECG-electrocardiogram; ChEIs-cholinesterase inhibitors

Medications that may contribute to cognitive decline should be identified.[1,3,52] (See table 5).

Table 5: Medications associated with cognitive impairment in the elderly[52]

- 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
- Antiparkinsonian drugs – risk is highest in those with anticholinergic activity
- Antidepressants – risk is highest with tricyclic antidepressants
- Anticonvulsants – all anticonvulsants can impair cognitive function
- Cardiac drugs – including digoxin (dose related), disopyramide, calcium antagonists
- Corticosteroids – the risk is dose related

Referral for specialist input (e.g. from Old Age Psychiatry, Gerontology, Neurology and Memory Clinics) should be considered to confirm the diagnosis, exclude other pathologies and identify the dementia subtype.[1,3] Structural imaging such as CT or MRI is used to exclude other cerebral pathologies (e.g. intracranial neoplasm or normal pressure hydrocephalus) and to differentiate the dementia subtype;[1,3-5] single photon emission tomography (SPECT) or PET imaging can differentiate between AD, VaD and FTD.[26] Investigations such as CSF analysis and EEG are not routinely undertaken but may be considered for atypical presentations.[3-5,46]

MANAGEMENT

The first step in the management of dementia is a timely diagnosis, and disclosure of the diagnosis in a sensitive way to the patient and their family/carer as appropriate.[3,16] Disclosure of the diagnosis has been shown to decrease depression and anxiety in patients and their family/carers.[16] Patients and their family/carers should be informed of the dementia subtype, the HCPs involved in their care, medico-legal issues, local support groups and the effect of dementia on driving if appropriate.[3,16] **A patient-centred approach is recommended to enable the patient to stay living at home for as long as possible.**[1-3] If possible physicians may encourage patients to draw up advance directives containing future treatment and care preferences.[3,16] People with dementia present with complex problems and experience symptoms in many domains including cognition, neuropsychiatric symptoms, ADL and they may also have co-morbidities;[4] the patient's needs will change with time.[4] Multidisciplinary input from HCPs include GPs, neurologists, geriatricians, pharmacists, public health nurses, physiotherapists, occupational therapists, speech and language therapists, social workers, dietitians and psychologists. **Educational resources on dementia in primary care** include "Dementia Pathways" which is a useful online educational resource directed at GPs and HCPs in primary care for the diagnosis and management of people with dementia (available at www.dementiapathways.ie), and the Irish College of General Practitioners guideline on "Dementia: Diagnosis and Management in General Practice" (available at www.icgp.ie) – see Useful Resources (table 7).

NON-PHARMACOLOGICAL THERAPIES

People with dementia and their families/carers require emotional and practical support to help them live as good a quality of life as they can; the GP is in a key position to provide ongoing support and advice.[5,26] **Patients should be offered a range of activities individualised to their needs to promote their well-being.**[3] Therapies such as group cognitive stimulation which improves cognition in patients, and individual cognitive rehabilitation or occupational therapy, which may improve functional ability, could be considered for people with mild to moderate dementia.[3,4,53] **Exercise improves the ability to perform ADLs in people with dementia; it is also beneficial for cardiovascular and cerebrovascular health, diabetes, obesity, and it protects against frailty.**[4,54] Families usually provide most of the care to people living at home, which can be psychologically and physically demanding;[4] **approximately 40% of family/carers have clinically significant depression or anxiety.**[4] Voluntary organisations such as the Alzheimer's Society of Ireland provide a wide range of information sources and practical support for people living with dementia (see useful resources - Table 7).

PHARMACOLOGICAL THERAPIES

Currently two classes of drugs are used for specific types of dementia; **these drugs do not modify the underlying neuropathology or the progression of dementia.**[4] Cholinesterase inhibitors (ChEIs) (donepezil, rivastigmine and galantamine) delay the breakdown of acetylcholine released into synaptic clefts, thereby enhancing cholinergic neurotransmission. Memantine is a N-methyl-D-aspartate receptor (NMDA) antagonist; overstimulation of NMDA is implicated in neurodegenerative disorders.[1,26,55] Table 6 summarises the drugs authorised for use in dementia; the Summary of Product Characteristics (SmPC) of each medicine should be consulted for full prescribing information, including adverse effects.

Table 6: Indications and special precautions of drugs used in dementia*[56-59]

Drug	Indication	Special Precautions include*
Donepezil tablet	Mild to moderate AD	ADRs may be dose-related and occur on initiating treatment and/or ↑dose (may respond to ↓ dose); vagotonic effects on heart (e.g. bradycardia), caution in conduction disorders and CV disease; associated with weight loss (monitor weight); may cause ↑ gastric acid secretion (care in patients at risk of/with PU); care in patients with asthma or COPD; may cause seizures and bladder outflow obstruction. Risk of drug interactions – refer to SmPC of each medicine* Application site reactions may occur with rivastigmine patch
Rivastigmine capsule transdermal patch	Mild to moderate AD and PDD	
Galantamine tablet/capsule oral solution	Mild to moderate AD	
Memantine tablet oral solution	Moderate to severe AD	Use with caution in patients with epilepsy; avoid co-administration with NMDA antagonists e.g. amantadine, ketamine, dextromethorphan

AD-Alzheimer's disease; ADRs-adverse drug reactions; PDD-Parkinson's disease dementia; CV-cardiovascular; PU-peptic ulcer; COPD-chronic obstructive pulmonary disease; SmPC-summary of product characteristics; NMDA-N-methyl-D-aspartate receptor; *full prescribing information including adverse effects is available in the Summary of Product Characteristics

Practical aspects of pharmacological therapy

Cholinesterase inhibitors are licensed for mild to moderate AD; they result in modest improvements in cognitive function and may also be beneficial for improving the ability to perform ADL and behaviour.[4,26,55,60] Efficacy seems to be

similar between the ChEIs.[26,56,61] Evidence supports the continuation of ChEIs as the disease progresses, if there is a beneficial effect on cognitive function; discontinuation may be associated with cognitive and functional decline, and may result in earlier transfer to a nursing home.[4,26,62,63] A trial discontinuation of ChEIs should be considered for patients who have taken a ChEI for >12 months, and where 1) the patient's cognition and/or function has declined significantly over the past 6 months, 2) no benefit has been seen at any time during treatment, and 3) the patient has severe/end stage dementia; patient/family preference and the presence of significant adverse effects, should also be included in the decision.[41,65,66] The dose should be tapered before stopping treatment and the patient monitored over the next 1 to 3 months; if cognitive decline occurs on discontinuation, consideration should be given to reinstating therapy.[41,66] **Individual dose titration of ChEIs is recommended; adverse effects (e.g. gastrointestinal) may be reduced or avoided by slow up-titration of the dose.**[1,64] Switching between the ChEIs has been shown to be of benefit in up to 50% of patients who cannot tolerate the first agent.[26] Evidence supports ChEI use (e.g rivastigmine and donepezil [unauthorised for this indication]), in patients with mild to moderate DLB and Parkinson's Disease dementia (PDD).[4,26,64,67-69] ChEIs are not recommended in patients with VaD, unless the patient has mixed dementia.[3,26] **Cardiovascular risk factors should be managed in patients with VaD.**[26] Evidence does not support ChEI use in patients with FTD.[3,4,26,34,46] **ChEIs have not been shown to be effective for MCI.**[4,26,70]

Memantine has beneficial effects on cognitive function and functional decline in moderate to severe AD.[4,26,71] Memantine is also recommended for patients with moderate AD who are intolerant of or who have a contraindication to ChEIs.[1,3,4] **Combination therapy of ChEIs and memantine may also be considered in patients with moderate to severe AD.**[1,3,26]

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)

The term BPSD is used to describe a range of behavioural and psychological symptoms (e.g. agitation, depression, apathy, psychosis, aggression, anxiety and insomnia) experienced by patients with dementia.[1,34,72] BPSD occurs in up to 90% of people with dementia;[73] **it is associated with declining cognitive and functional ability, family/carer stress and increased institutionalisation.**[34,72] Assessment for BPSD should take place at dementia diagnosis and at regular intervals thereafter.[46] Assessment requires a thorough history from the patient, their family/carers and should include the patient's: 1) physical health (e.g. pain, infection and constipation), 2) mental health, 3) side effects of medication, 4) pre-morbid personality, 5) psychosocial factors and 6) environmental factors.[1] **Co-morbidity, unmet needs (e.g. pain, fear, boredom) and environmental triggers should always be excluded as a possible cause for the underlying symptoms.**[3,34,72,74] In particular it is important to identify and treat delirium (occurs in >50% of patients with dementia), as treatment of the delirium will often relieve the symptoms of BPSD.[4,11]

Non-pharmacological management should be considered as first line treatment for BPSD,[1,3,46,72,74] after acute medical conditions have been excluded and/or treated. These include reminiscence therapy, multisensory stimulation (e.g. music therapy), simulated presence therapy, and interventions for family/carers (e.g. education and support).[41,72,74,75]

Pharmacological therapy is indicated for BPSD when non-pharmacological approaches are unsuccessful, there is a risk of self-harm or harm to others and the patient is experiencing agitation, hallucinations or delusion that are causing them severe distress.[1,3,4,72] Antipsychotics are used in 20 to 50% of patients with dementia;[76] atypical antipsychotics (including risperidone [the only medicine licensed for BPSD[77]], aripiprazole and olanzapine) have the strongest evidence for use.[72,76] **Antipsychotics are associated with an increased risk of adverse effects including extrapyramidal symptoms, cerebrovascular events (in particular with the atypical antipsychotics) and mortality.**[4,72,76,78,79] The mortality associated with typical antipsychotics (e.g. haloperidol) appears to be up to twice that with risperidone, with greater risk at higher doses.[4,72] **Antipsychotics should only be prescribed if non-pharmacological approaches have failed and if considered absolutely necessary; they should be used at the lowest effective dose for the shortest possible time**; patients should be reassessed regarding the need for continued use every six weeks.[3,4,80] **Antipsychotic use in patients with LBD and PDD may exacerbate the motor features and cause severe antipsychotic sensitivity reactions.**[3] Nearly all antipsychotic medication is associated with QT prolongation (see individual SmPCs); an ECG should be considered.[80]

Other therapies such as citalopram (unlicensed use) may reduce agitation,[81] but have important adverse effects including QT prolongation, cognitive impairment and increased risk of falls.[4,72] There is inconsistent evidence regarding the benefits of ChEIs and memantine for BPSD.[41,72,74,82-86] There is a lack of evidence supporting the use of antidepressants in patients with depression in those with dementia;[4,72] they should not be routinely offered for patients with mild to moderate depression unless there is a pre-existing severe mental health problem.[3]

In summary, this bulletin provides an update on the management of dementia. Table 7 provides information on other useful resources.

Table 7: Useful resources

Useful resources for Healthcare Professionals (HCPs) include:

- Dementia Services Information and Development Centre (St James's Hospital) – National centre for excellence in dementia, offers services in education and training, information and research available on www.dementia.ie
- Dementia: Diagnosis and Management in General Practice published by the ICGP in March 2019 – available on www.icgp.ie
- Primary Care Research, Education and Pathways of Dementia (PREPARED) project (UCC) – range of clinical educational resources directed at HCPs in primary care available on www.dementiapathways.ie

Useful resources for HCPs, patients and carers include:

- The Alzheimer Society of Ireland available on www.alzheimer.ie
- Dementia – Understand Together available on www.understandtogether.ie
- Family Carers Ireland available on www.familycarers.ie

List of references available on request. Date of preparation: April 2019

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