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Dementia: Module 1

Recognition and management of mild cognitive impairment

Based on Prof Potocnik's talk at the Cipla Psychiatry Forum, Kleinmond, Cape Town on 11-13 October 2019

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LEARNING OBJECTIVES

You will learn:

1. How to advise patients on lifestyle factors that might delay or reduce the risk of developing mild cognitive impairment (MCI) associated with aging
2. To recognise and diagnose MCI
3. To provide pharmacological management of MCI.

Introduction

Not all patients observed by clinicians as experiencing declining memory will progress to dementia; nonetheless these individuals, who make up the majority of patients, will benefit from appropriate intervention (Table 1).

Ongoing follow-up will eventually clarify whether the individual patient will progress to dementia or not. Currently, diagnostic techniques such as cerebrospinal fluid (CSF) analysis and advanced neuro-imaging techniques (computerised PET scans) or amyloid traces would help differentiate between patients but are not readily available in South Africa.

So, in order to provide benefit and preemptively preserve complex instrumental activities of daily living (use of communication tools, transport, managing medication and own finances) early treatment is warranted.

The decline in cognitive ability varies from one individual to another (Table 2).

Table 1. Ageing and mild cognitive impairment (MCI)

• 10% of patients with MCI – will get better
• 10% of patients with MCI – remain stable
• 10% of patients with MCI – will progress to dementia
Therefore:
• 70% of the 'young old' (<75 years) don't develop dementia
• Ageing >75 years increases rates with more than 40% of 100-year-olds exhibiting dementia.

Table 2. Clinical and lifestyle risk factors for age-related cognitive decline[1,2]

• Family history/genetics
• Vascular disease and associated risk factors – High blood pressure – Smoking – Diabetes – Obstructive sleep apnoea – Atrial fibrillation
• Psychological health, e.g. depression, anxiety, mental stress
• Exposure to inappropriate medications
• Nutrition – B vitamins, antioxidants (fruits and vegetables), omega-3 fatty acids (oily fish) may be protective – Refined carbohydrates, sugars, cholesterol, trans-fats are associated with poorer outcome – High alcohol consumption – Physical inactivity – Poor sleep – Education: Longer duration of formal education is associated with less cognitive decline; a lower level of education is associated with increased risk – Social class: higher social class (which may be indicative of exposure to expertise and better access to healthcare) is associated with less cognitive decline – Lack of cognitive stimulation.

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Mild cognitive impairment and functional decline

The mini mental state examination (MMSE) is a widely used screening tool for early dementia, depending on level of education. A score of between 24 and 27 (out of a maximum of 30) is considered abnormal and indicative of MCI.[3] A declining score on the MMSE is associated with a commensurate decline in function. MCI is indicated by consistent cognitive impairment in one or more domain (e.g. memory, language, behaviour) that is noticeable to the patient or their family or caregivers, but which does not affect daily activities. Memory relative to age and education and scores on tests of intellectual function may be normal. The onset of symptoms is variable and often unclear. Symptoms can include apathy, agitation, anxiety, irritability, delusions and hallucinations.[4] In approximately one in three people with MCI, cognitive impairment is progressive.

It is increasingly being recognised that MCI is often associated with recognisable deficits in complex instrumental, social and cognitive activities of daily living, the presence of which predict an increased risk of progressive dementia. These impairments may be unrecognisable to the patient and are often reported by a family member or caregiver. Examples include using the telephone, driving skills and making local travel arrangements, correct use of medication and personal financial management. Restriction in at least two of these activities is associated with increased risk of a clinical diagnosis of dementia within 3-10 years and more rapid functional deterioration over time.[5,6]

In the same way as we supplement diminishing hormone levels by, for example, providing hormone replacement therapy in women or testosterone in men, so should we, as clinicians, supplement declining memory

Pharmacological management of MCI

Early treatment of MCI can reduce progression, improve quality of life, delay the necessity for institutionalisation and allow patients and caregivers to prepare for an inevitable outcome (e.g. lifestyle changes, driving ability, advance directives, will preparation).

1. Hormone therapy (HT)

Provided it is initiated at the time of menopause, that a deficiency of female hormones has been clearly established and it is initiated before the onset of dementia symptoms, oestrogen or combined oestrogen/progestin HT may be beneficial in delaying the onset of dementia by 2-3 decades. Treatment duration is usually not longer than two years.

2. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Conventional NSAIDs (e.g. ibuprofen, diclofenac) used for more than 2-3 years may be protective.

3. Cognitive enhancers

Because cognitive deterioration is associated with progressive loss of cholinergic neurons and decreasing levels of acetylcholine in the brain, drugs that inhibit the breakdown of acetylcholine (acetylcholinesterase inhibitors) or enhance cholinergic activity may reduce the progression of cognitive decline if used early enough (Table 3). Tolerability is improved by starting with a low dose at night (except galantamine) and increasing the dose only after four weeks, according to efficacy and tolerability. Side effects include mild sedation (initially), abdominal discomfort, anorexia, nausea, vomiting, diarrhoea, dizziness, postural hypotension, anxiety, insomnia, vivid dreams, depression, increased salivation, sweating, and cramps. Because the mechanism of action of anticholinesterase inhibitors differs, when side effects are unacceptable on one (e.g. excessive salivation with drooling, severe ongoing diarrhoea or abdominal cramps) tolerability may be improved by switching to another.

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that regulates calcium flux across

membranes and may protect against neuronal death associated with excitotoxicity. Potential adverse effects include confusion, dizziness, headache, tiredness, and enhancement of L-dopa and dopaminergic agonists (Table 4).

A combination of an acetylcholinesterase inhibitor with memantine may be more effective than either agent alone. It allows for the use of low doses and is well tolerated (Box 1). Treatment should be started as early as possible, as soon as there is any suspicion of MCI, which may be before there are demonstrable impairments on the MMSE. Even subtle improvements in cognitive state, such as return of personality, spontaneity, insight and interest in surroundings, are often noticeable, improving the wellbeing of both patients and their caregivers and reducing the associated healthcare costs.

Table 3. Cognitive enhancers[7]

Agent	Mechanism of action	Half-life	Dose
Donepezil	Selectively inhibits acetylcholinesterase	70 hours	Start dose: 2.5mg nocte one month Total dose: 5-10mg mornings
Galantamine	Selectively inhibits acetylcholinesterase and also modulates activity of nicotinic receptors	>24 hours	Start dose: 8mg mornings Total dose: 16-24mg daily

So, in order to provide benefit and pre-emptively preserve complex instrumental activities of daily living (use of communication tools, transport, managing medication and own finances) early treatment is warranted.

Table 4. Memantine

NMDA receptor antagonist half-life: 60-100 hours
Amantadine derivative
Dose titration schedule (1 tab = 10mg)
Mornings
- Week 1: ½ tab
- Week 2: 1 tab
- Week 3: 1½ tabs
- Week 4 onwards: 2 tabs

Box 1. Starting regimen for combined memantine plus donepezil, initiated three months apart

Start memantine (1 tablet = 10 mg): Month 1: ¼ tablet at night; Month 2: ½ tablet at night
Start donepezil (1 tablet = 10 mg): Month 1: ¼ tablet at night; Month 2: ½ tablet in the morning

In addition to the cognitive enhancers, further pharmacotherapy should be individualised to the evolution of the patient's mood and behavioural symptoms over time. Other medical or psychiatric causes of these symptoms should also be excluded, including side effects of medication.

4. Antidepressants

A trial of antidepressant medication is indicated in patients where comorbid depression or anxiety is suspected. Lower doses may be appropriate in older patients and sedating antidepressants (e.g. citalopram, sertraline, mirtazapine, agomelatine) are preferred. Tricyclic antidepressants are not recommended.

General principles for the use of psychotropics in the elderly are listed in Table 5. Treatment should be initiated with low doses (generally one-half to two-thirds of the usual adult dose), with gradual titration against efficacy and tolerability, and frequent review. Polypharmacy is often required and, where necessary, patients should be advised to use a pill cutter to avoid irregular and under- or over-dosing.

Table 5. General principles for use of psychotropic medications in the elderly[8]

- Use one-half to one-third of the usual adult dose
- A pill cutter is essential
- Start low, go slow and review frequently
- The elderly are more sensitive to medication side effects than younger adults
- Polypharmacy may be necessary
- Psychoeducation with regard to illness and supervision of medication are essential
- Data pertaining to medication use in the elderly are, in general, controversial

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5. Antipsychotics

Indications for considering an antipsychotic include psychotic symptoms, restlessness, agitation and insomnia. Appropriate combination of antipsychotics (e.g. risperidone plus quetiapine) allows for lower doses with fewer side effects, better tolerability and targeting of symptoms. Where aggression, psychosis, resistance to care or restlessness is prominent, low-dose risperidone is the agent of choice, but must be administered during the daytime (usually at 08h00 and 17h00 if using twice daily dosing). Where necessary, it may be combined with chlorpromazine/quetiapine at night (administered at 20h00). An alternative to these combinations is monotherapy with olanzapine given at 17h00 (Table 6).[8]

Table 6. Example of a neuroleptic regimen for elderly patients[8]

Risperidone 0.25-0.5mg twice daily during the day (usually administered at 08h00 and 17h00); if necessary, increase the dose to 0.75mg, 1.0mg and 1.5mg twice daily for daytime control. Wait a day or two between dose increases.
Together with
Chlorpromazine or quetiapine 25mg at night (at 20h00); if necessary, increase dose to 50mg, 75g and 100g at night for nocturnal control. Wait a day or two between dose increases.
Or
Olanzapine 2.5-10mg in the late afternoon (at 17h00)

6. Hypnotics

In a psychotic patient, lorazepam is the drug of choice for acute sedation. However, in general, because of an increased frequency of daytime somnolence, emotional lability, confusion, incoordination, memory impairment and incontinence, benzodiazepines should be avoided. Preferable choices for short-term management of insomnia include zolpidem or zopiclone, or a sedating antidepressant or sedating neuroleptic agent, such as chlorpromazine, olanzapine or quetiapine.

7. Others

Clonazepam may be helpful for restless leg syndrome and for mild vocalisers. For more disturbing vocalisers, a combination of clozapine and amisulpride is usually indicated. Cyproterone acetate is effective for paraphilia, causing a reduction in sexual disinhibition or hypersexuality within a few days.

KEY LEARNINGS

- Age-related cognitive decline varies from one individual to another, dependent on clinical and lifestyle risk factors
- Early individualised pharmacological management of MCI can reduce progression to dementia and improve quality of life
- Drugs that inhibit the breakdown of acetylcholine or enhance cholinergic activity may reduce the progression of cognitive decline
- It is recommended that lower doses of psychotropic and antidepressant medications be used in older dementia patients at initiation of treatment
- Benzodiazepines should be avoided in the psychotic dementia patient.

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