

# Dementia

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## 1. Introduction

By definition, dementia is an acquired global impairment in memory, personality and intellect in an alert patient, that is sufficiently severe to interfere with social and/or occupational functioning. In the absence of a stroke or rapidly growing cerebral tumours (among other causes), the onset is usually gradual and the cognitive decline is always progressive. In the absence of a cure for the disease, non-pharmacological interventions and the judicious use of pharmacotherapy may not only help the patient and alleviate the stress on the caregiver, but can also help in delaying institutionalisation.

### 1.1 Prevalence and burden of disease

The worldwide prevalence of dementia currently approximates 35.6 million people, a figure set to rise to 65.7 million by 2030 and (by doubling every 20 years) to 115.4 million by 2050. Nearly two-thirds of individuals with dementia live in developing countries, where the sharpest increase in numbers is said to occur.<sup>[1]</sup> The prevalence of dementia is approximately 5 - 7% of the elderly population. Starting at 1% for 60-year-olds, the prevalence doubles every 5.1 years, rising to some 30 - 45% of those aged 85 and older<sup>[2,3]</sup> in developed countries, while doubling every 7 years in developing countries.<sup>[4]</sup> Among the South African elderly an estimate would place the number of dementia sufferers at 250 000, with some 35 000 of these suffering from Alzheimer's disease (AD).

Twenty per cent of AD patients are alive after a 15-year period, the mean duration of illness being some 10 - 12 years.<sup>[5]</sup> Of the people with late-onset (65 years and older) dementia in developed countries, more than half have AD, some 15% have vascular dementia (VaD), and the remaining 30%, a variety of some 60 other forms of dementia.<sup>[6]</sup> Many cases of AD exhibit a confluence with cerebrovascular disease (CvD).<sup>[7]</sup> The total worldwide societal cost of dementia was estimated at US\$422 billion in 2009, which included US\$142 billion (34%) for informal care.<sup>[8]</sup> Americans estimate that dementia costs them some US\$100 billion per year,<sup>[1]</sup> and yet a delay in the onset of AD by only 5 years would halve the prevalence of the disease, resulting in enormous savings of human misery and cost to society.<sup>[5,9]</sup> In all cases there are profound psychosocial effects on the caregiver, in whom the rates of depression, substance abuse, hospitalisation and physical illness are all increased.<sup>[9]</sup>

### 1.2 Causes and types of dementia

In the South African population, dementia due to the HIV/AIDS complex (affecting mainly the younger age group) is the most common. Among the elderly the most prevalent is VaD, followed by AD, which is on the increase.<sup>[7]</sup>

#### 1.2.1 Alzheimer's disease

The neuropathological hallmarks of AD are amyloid plaques, neurofibrillary tangles, and synaptic and neuronal loss with

subsequent brain atrophy. Macroscopically, and with neuro-imaging (magnetic resonance imaging (MRI) and computed tomography (CT) scan), this demonstrates as flattening of gyri, widening of sulci, atrophied medial temporal lobes and enlarged ventricles. Pathology at microvascular level has increasingly been implicated in the aetiology of AD, blurring the boundaries with VaD in many cases. AD and possibly most other dementias tend to follow a sinusoidal course in that the initial slow, progressive deterioration accelerates rapidly before flattening out towards the end – in keeping with the 3 stages of mild, moderate and severe.<sup>[10]</sup>

The duration of illness may be as short as 6 months or as long as 20 years, with an average of 12 years. Neurochemically there are deficits in neurotransmitters including acetylcholine, noradrenaline, serotonin, and somatostatin. Specific mutations on chromosomes 21, 14 and 1, inherited as familial autosomal dominant traits with full penetrance, are found in some 1% of all AD patients. Here the illness usually presents itself in the 40s or early 50s and is essentially 'pre-senile' in onset (i.e. before the age of 65 years). More than 90% of cases of AD occur in individuals older than 60 years. Individuals carrying one or both alleles coding for apolipoprotein E-4 (APOE4) on chromosome 19 bear an elevated risk for late-onset AD, although this gene is not itself a cause of the disorder.<sup>[11]</sup> Fig. 1 represents the course of AD.

#### 1.2.2 Vascular dementia – with or without stroke

Among the VaDs, multi-infarct dementia associated with multiple areas of cortical infarction, patchy cognitive impairment, focal neurological signs and a 'stepwise' rather than a steady, continuous deterioration as in AD is more easily diagnosed than dementia due to vascular damage of the deep white matter.

After each shower of 'mini strokes', which produce a sudden deterioration in the individual's functioning, there is a partial recovery which stabilises within approximately 3 - 12 weeks until the next stroke or 'step' occurs several weeks or months later. It is hypothesised that in both vascular and alcohol-induced dementias, temporary vascular spasms may result in intermittent or fluctuating intellectual

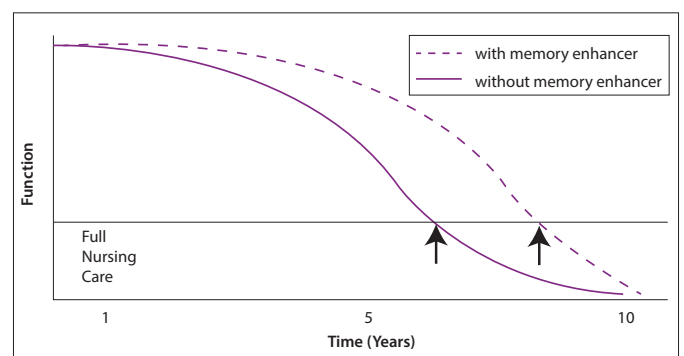


Fig. 1. Course of Alzheimer's disease (with/out memory enhancer).<sup>[10]</sup>

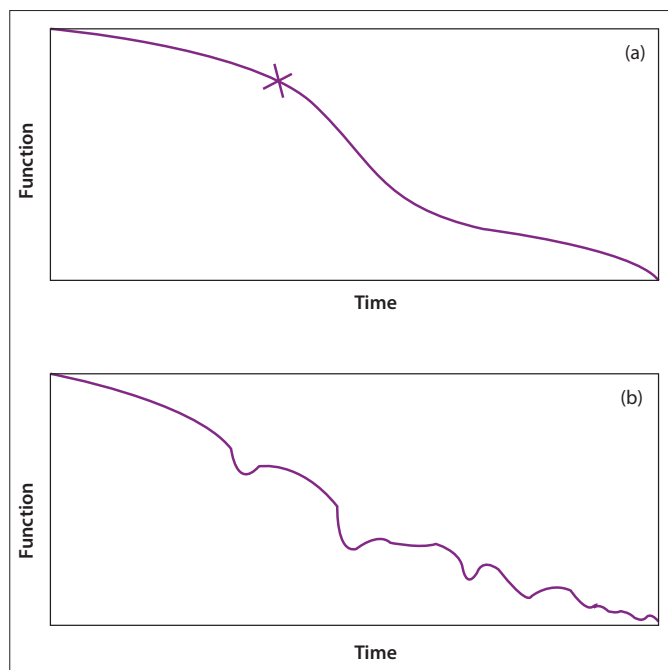


Fig. 2. Course of (a) Alzheimer's disease and (b) vascular dementia.<sup>10</sup>

and personality changes, with unpredictable bouts of irritability and mood swings. In all types of VaDs the risk factors for stroke such as hypertension, arrhythmias, hypercholesterolaemia, diabetes, smoking and alcohol need to be assessed. Fig. 2 represents the course of multi-infarct dementia compared to AD.

### 1.2.3 Combination of Alzheimer's disease and vascular dementia

This is referred to as AD with CvD.

### 1.2.4 Dementia with Lewy bodies

Dementia with Lewy bodies usually exhibits as fluctuations in cognition (mimicking a sub-acute delirium) with pronounced variation in attention and alertness, recurrent well-formed visual hallucinations (especially sun-downing), and motor features of Parkinsonism. The course of the illness tends to be rapidly progressive, interspersed with repeated falls, syncope, transient loss of consciousness, other hallucinations and congruent delusions. These patients tend to be sensitive to the side-effects of neuroleptic agents (requiring utilisation of drugs like clozapine or newer neuroleptic agents). They may be responsive to cholinesterase inhibitors.

### 1.2.5 Pick's disease and frontotemporal dementia

Pick's disease (PD) is a progressive dementia that chiefly affects the frontal cortex. PD most commonly manifests between the ages of 50 and 60 years and is distinguished from frontotemporal dementia by the presence of characteristic intraneuronal argentophilic Pick inclusion bodies found at autopsy. Patients present with prominent personality changes and impaired executive function. In frontotemporal dementia diagnostic criteria range across 4 domains:

1. Behavioural disorder: insidious onset and slow progression; early loss of personal and social awareness; early signs of disinhibition; mental rigidity and inflexibility; and hyperorality, stereotyped and perseverative behaviour.

2. Affective symptoms: depression and anxiety; somatic preoccupation; emotional unconcern.

3. Speech disorder: reduction and stereotypy of speech; echolalia and perseveration.

4. Physical signs: early primitive reflexes and incontinence; late akinesia, rigidity and tremor.

### 1.2.6 Substance-induced persisting dementia

Paramount are deep white-matter changes blurred with alcohol-induced vasculopathy, clinically often indistinguishable from VaDs and with the same risk factors as precipitating and perpetuating causes. Note that both vascular and alcohol-induced dementia patients have relatively well-preserved personalities, compared to the degree of dementia present. Their excellent social skills or verbal ability may be misleading unless one screens for dementia using the Mini Mental State Examination (MMSE).

### 1.2.7 Huntington's disease

Huntington's disease is an inherited disease (autosomal dominant gene on chromosome 4) characterised by degeneration of the basal ganglia and cerebral cortex. Age of onset is between 15 and 50 years, when choreiform movements and progressive dementia are noted. The dementia initially presents as a sub-cortical dementia before affecting the cortex as the illness progresses. No cure is currently available and death results within 15 - 20 years. Psychiatric disorders, especially depression, may be the presenting feature.

### 1.2.8 Parkinson's disease

The primary features are tremor, muscular rigidity, hypokinesia and postural abnormality. Although a movement disorder, cognitive impairment occurs in 10 - 40% of patients during the course of the disease, known as Parkinson's disease dementia.

### 1.2.9 Creutzfeldt-Jakob's disease

Creutzfeldt-Jakob's disease is brought about by a virus-like infective agent called a prion. It causes a rapid progressive dementia also affecting the pyramidal and extrapyramidal systems. A new variant of Creutzfeldt-Jakob's disease, described in England in 1995, appears to express itself under certain conditions in individuals under the age of 40 years, leading to death within a year. This variant is associated with bovine spongiform encephalopathy or 'mad cow disease'.

### 1.2.10 Dementia associated with normal pressure hydrocephalus

Normal pressure hydrocephalus occurs in the elderly and is characterised by a triad of ataxia (wide-based, shuffling gait), urinary incontinence and dementia. CT scans of the brain show prominent enlargement of the ventricles out of keeping with the widening of the sulci. Ventricular peritoneal shunts may improve cognitive functions in 10 - 30% of patients. Usually a demented person only becomes incontinent on attaining an MMSE score of 8 - 10/30.

### 1.2.11 Dementia secondary to head injury

This is lesion-location- and severity-specific, and diagnosed and treated accordingly. It may manifest with 2 distinct symptom clusters, namely cognitive impairment (i.e. decreased information processing speed, decreased attention, increased distractibility) and behavioural

disturbances. The behavioural disturbances may involve personality changes, impulsivity and depression, all of which can be exacerbated by substance misuse.

### 1.2.12 AIDS dementia complex/HIV dementia

HIV infection currently affects 5 million people in South Africa and is set to reach a steady state of 32% within less than a decade. The course of the illness may vary considerably but in general the patient converts to AIDS after 9 years of illness and dies a year later from systemic complications. Nearly 90% of AIDS brains are histopathologically abnormal, more than half of them uniquely due to HIV infection. Referred to as the AIDS dementia complex, this condition contributes significantly to the morbidity of HIV patients, causing varying degrees of cognitive, motor or behavioural impairment, known as HIV-associated neurocognitive disorders (HAND).

### 1.2.13 Other less common causes of dementia

- Endocrine states (hypo- or hyperthyroidism, hyperparathyroidism)
- Deficiency states (B complex vitamins)
- Intracranial space-occupying lesions (subdural haematomas, tumours)
- Post-irradiation dementia
- Demyelinating disorders
- Neurosyphilis

## 2. Diagnosis, clinical characteristics and course

The diagnostic criteria for AD are outlined in Table 1.<sup>[11]</sup>

Clinical features include the following:

- **Memory impairment:** Poor memory must interfere with daily functioning. Initially, short-term memory is affected, with the later involvement of long-term memory.

- **Personality and behavioural changes:** Emotions are shallow and easily influenced by environmental factors; irritability and bouts of anger are common. Usually premorbid traits become more accentuated. There is a loss of initiative and the person becomes increasingly apathetic and withdrawn. Emotional blunting ensues, and may be mistaken for depression.
- **Intellectual impairment:** Thinking becomes more concrete. There are word-finding and other language difficulties (dysphasia), the person may no longer recognise familiar faces or objects (agnosia) and may be unable to carry out simple manual tasks such as fixing a plug or dressing themselves (apraxia). A key feature is the instrumental impairment of activities of daily living (e.g. ability to use telephone, shop, handle finances).
- **Physical changes:** As the disease progresses, the patient appears unduly frail and weak, is stooped in posture with slow, shuffling gait and mild tremor of the hands. There is weight loss, regardless of appetite, increasing bouts of restlessness and confusion, and reduced sphincter control.

### 2.1 Course

This may give an indication of aetiology. Patients with vascular (especially multi-infarct) dementia and to some extent alcohol-induced dementia will present with patchy memory loss and fluctuating disturbances in language and behaviour with a relatively well-preserved personality in the earlier phases, characterised by appropriate social interaction.

- A step-wise deterioration rather than a steady even pattern
- A more abrupt deterioration rather than slow, insidious onset
- Attacks of dizziness, frequent falls and fainting spells, nocturnal confusion
- Bouts of urinary urgency, particularly at night.

**Table 1. Diagnostic criteria for dementia of the Alzheimer's type<sup>[11]\*</sup>**

- A. The development of multiple cognitive deficits manifested by both:
  1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
  2. One (or more) of the following cognitive disturbances:
    - a. aphasia (language disturbance)
    - b. apraxia (impaired ability to carry out motor activities despite intact motor function)
    - c. agnosia (failure to recognise or identify objects despite intact sensory function)
    - d. disturbance in executive functioning (i.e., planning, organising, sequencing, abstracting)
- B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
- C. The course is characterised by gradual onset and continuing cognitive decline.
- D. The cognitive deficits in criteria A1 and A2 are not due to any of the following:
  1. Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumour)
  2. Systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin B<sub>12</sub> or folic acid deficiency, niacin deficiency, hypercalcaemia, neurosyphilis, HIV infection)
  3. Substance-induced conditions
- E. The deficits do not occur exclusively during the course of a delirium.
- F. The disturbance is not better accounted for by another Axis I disorder (e.g. major depressive disorder, schizophrenia).

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### 3. Assessment and differential diagnosis

#### 3.1 Mild cognitive impairment

Of note is that up to one-quarter of elderly present as 'dodderly', falling into the realm of mild cognitive impairment (MCI), also known as age-associated cognitive decline. Here the MMSE score is around 27/30. Cognitive function is not impaired to the point where it interferes significantly with daily social or occupational functioning, but may well do so over the next 2 - 5 years, when an estimated 30% of this category are known to go on to exhibit dementia. These patients need to be re-evaluated at regular intervals.

#### 3.2 Depression and delirium

At this stage of diagnostic screening dementia must be distinguished from depression (primarily a mood disorder with very little disturbance in cognition), and delirium (a transient organic disorder hallmarked by a global cognitive impairment as well as disturbance in consciousness and attention/concentration deficit). In addition there is a reversal of the sleep-wake cycle. In the elderly, depression and delirium may frequently coexist with AD or herald its presence, and both require management in their own right. Delirium constitutes a medical emergency. Good collateral information from a reliable family member, friend or caregiver is crucial. A detailed history and thorough physical examination including blood ('organic work-up') and urine tests not only distinguish AD from depression and delirium, but also help to differentiate AD from other types of dementia. A review of all current prescribed medications and over-the-counter preparations, with particular emphasis on those impacting on central nervous system functions, is essential.

#### 3.3 Assessment of neuropsychiatric symptoms

This is discussed below.

##### 3.3.1 Cognitive assessment: the Mini Mental State Examination

Ascertain the degree of cognitive impairment by administering the MMSE,<sup>[12]</sup> which was designed to distinguish dementia from depressive pseudodementia. While one or two mistakes are allowed, the nature of these mistakes is of importance (e.g. an accountant failing to do the serial sevens). An MMSE score of 27 generally indicates MCI. In mild AD (MMSE range 21 - 26) there is short-term memory impairment, often accompanied by symptoms of anxiety and depression. Moderate AD (MMSE range 11 - 20) is characterised by neuropsychiatric phenomena such as visual hallucinations, false beliefs, restlessness and disturbed sleep patterns. Severe AD (MMSE range 0 - 10) is characterised by prominent cognitive decline, motor signs and the onset of loss of sphincter control.

While depressed patients will still obtain a high MMSE score, an MMSE score of 26 or less out of 30 is strongly indicative of dementia, where the patient has had at least 7 years of schooling. AD patients lose on average some 2 - 3 points on the MMSE per year, and progress can thus be tracked by re-administration of the test at 3 - 6-monthly intervals. There is no time limit for the completion of the test.

Note that a person with dementia may achieve an MMSE score of 30 out of 30 with some difficulty, while still holding a high position in working life. This function is support-staff dependent.

##### 3.3.2 Functional assessment: activities of daily living

Cognition and behaviour also impact on the patient's level of function.<sup>[13]</sup> This determines whether patients can still perform more complicated tasks such as taking their medication, difficult household chores, shopping, cooking and finances (instrumental activities of daily living (IADL)) or only wash, dress, feed and toilet themselves (basic activities of daily living (BADL)).<sup>[14]</sup> The watershed between IADL and BADL usually occurs at an MMSE of 16 out of 30,<sup>[15]</sup> while urinary incontinence occurs at a score of around 8.

##### 3.3.2.1 Driving

Driving a car relies on implicit memory, praxis and executive functioning. In the early stages of the illness patients can still drive a car because these abilities are still relatively intact. With time, however, they are unable to pay attention to all aspects of driving and often become impulsive or exercise the wrong options. Note that if the dementia renders the person incapable of driving and controlling a vehicle safely, he/she is medicolegally disqualified from driving. Doctors have a legal obligation under the National Road Traffic Act 1996 (Act 93 of 1996) to report such individuals to the traffic authorities.<sup>[16]</sup>

In general:

- Assess all cases on individual merit.
- Patients must drive in conditions affording good visibility and then in day time only, on non-busy suburban roads and always accompanied by a caregiver.
- Their MMSE should be at least 20-22/30 or above and they must still be able to do the pentagon test (which tests for visuospatial ability) or trail-making B.
- Re-assess at 3-monthly intervals.

##### 3.3.2.2 Firearms

Similarly gun licenses should be revoked for the same reasons.

##### 3.3.2.3 Financial affairs and wills

Should the patient be incapable of handling her/his own financial affairs, urge a reliable and trustworthy member of the family to take control of the situation. Transfer of authority by means of power of attorney works well in early dementia where competency is still preserved. Failing this, or where no family members are available, curatorship should be sought. The forms are obtainable from the court who will appoint a *curator bonis* to attend to the patient's affairs based on the recommendations of a psychiatrist and medical officer/general practitioner. Social workers and occupational therapists who are well-versed in these matters may have to be called in for advice and help with these cases. A patient who has not yet written a will or testament but now wishes to do so should be referred to a psychiatrist in order to establish testamentary capacity.<sup>[16]</sup>

##### 3.3.2.4 Social assessment

A thorough social evaluation is of the utmost importance when assessing a dementia patient. The social assessment includes information regarding where the person lives, living circumstances, relevant family members and caregivers, and the extent of coping of both patient and caregivers, employment (if relevant) and economic



resources, and degree of additional social support, as well as medicolegal matters.

### 3.3.2.5 Elder abuse

Awareness of abuse in the area of financial resources and the administration of the patient's affairs is of paramount importance. It should be determined who draws, administers and dispenses the patient's financial resources and pension.

Elder abuse includes physical abuse as well as 'acts of omission' or negligence leading to the detriment of the health and well-being of the person. This would include physical, psychological, financial and material aspects. Examples would be the denial of food, visits, medication, clothing and other essentials. Note that sexual abuse and incest also occur.

Cases must be reported to Halt Elder Abuse Line (toll free 0800 003081) for investigation and management.

### 3.4 Comorbid medical conditions

Patients with dementia commonly have comorbid medical conditions such as depression, cardiovascular and pulmonary diseases, infections, arthritis, sleep disturbances, falls, incontinence and drug-related adverse events, among others. There is a strong association between medical conditions and impaired cognition in AD.<sup>[17]</sup>

People with dementia, particularly those who live alone, are at risk of inadequate nutrition and dehydration. Both of these factors can contribute to the development of neuropsychiatric symptoms (NPS). The propensity to develop subsequent bronchopneumonia or urinary tract infection is very high.

Comorbid medical conditions need to be optimally managed, especially vascular risk factors which may be contributing to the dementia by exacerbating any vascular disease. Regular medication review is mandatory as is the supervision of medication by a responsible caregiver.

### 3.5 Investigations

Cost restraints and other practicalities often dictate the number of investigations that can be performed. Generally, in a typical or advanced case of dementia, investigations have little to offer towards treatment. A 'positive' result is more likely to be obtained when:

- The patient is less than 65 years of age
- Onset has been recent and the course rapid
- Course of disease fluctuates markedly
- Physical examination reveals a neurological deficit.

Special investigations help to improve or rule out treatable contributory and exacerbating causes of dementia. The full 'organic work-up' entails a full blood count, plasma viscosity, urea and electrolytes; thyroid, liver and parathyroid function tests, random blood sugar, niacin, vitamin B<sub>12</sub>, red cell folate and lipogram. C-reactive protein (CRP) levels may be indicated. Additional tests include syphilis serology, HIV and urine dipstick (this also helps to exclude a concurrent urinary tract infection).

More specialised investigations encompass a CT or MRI scan (with measurements of the medial temporal lobes) as well as psychometric testing. Single photon-emission CT results often settle diagnostic speculation.

Assessment by a trained neuropsychologist may be required when the cognitive impairment is very mild or does not conform to an expected pattern.

The trimmed-down version of the 'organic work-up' consists of the following only: haemoglobin, mean cell volume, white cell count and platelets; glucose; potassium, sodium and urea/creatinine; thyroid-stimulating hormone; albumin and gamma-glutamyl transferase (γGT); calcium; vitamin B<sub>12</sub>; total cholesterol; syphilis serology and urine dipsticks.<sup>[10]</sup>

## 4. Treatment

Patients with dementia almost invariably display neuropsychiatric symptoms (NPS), such as disturbances in mood with psychotic and vegetative symptoms among other phenomena.<sup>[18]</sup> Hitherto the focus with cognitive enhancers has been on cognitive improvement, overlooking the fact that these medications will often improve the NPS, especially in the early phases of the illness. Amelioration of these symptoms may be insufficient later on, at which stage treatment with more conventional psychotropic agents will be required.

### 4.1 Treatment goals

- Re-establishing the homeostasis, correcting for both internal and external factors by correcting influences such as dehydration, urinary tract infection, and disruptions in day/night rhythm.
- Stabilising the NPS to promote patient well-being and reduce caregiver burden.
- Maintaining the quality of life and highest level of patient functioning for as long as possible, in order to delay institutional care.

### 4.2 General aspects of treatment

As with the assessment process, treatment is holistic, by its nature multifaceted and, more often than not, multidisciplinary. Of necessity, the treatment involves caregivers and family. Team-work is essential and should utilise as many members from the community (helpful family members, religious groups) and medical resources (social worker, occupational therapist, community nurse) as possible. Patient target symptoms include declining cognition and impairment in daily functioning, among various associated symptoms that manifest during the course of the disorder. Treatment aims at maximising functional performance and quality of life, while reducing the period of disability.

#### 4.2.1 Imparting the diagnosis

Ensure that key family members and caregivers are present. Be compassionate, honest and leave sufficient time available for questions and answers in order to contain the situation. Keep hope alive in that there are treatments available for some dementias, and potential benefits from psycho-education, social support and medication trials. Apart from the diagnosis, include prognosis and management strategies. Keep an open-door policy, link up with the family physician and refer to the local support organisation.<sup>[19]</sup> Additional issues that need to be addressed include genetics and other practical and medicolegal decisions such as driving, firearms, power of attorney, financial controls, curatorship and wills, and capacity assessments (discussed above). Note that the detection of elder abuse, incapacity to drive and/or ownership of a firearm is notifiable by law.<sup>[16]</sup>

#### 4.2.2 Accommodation and level of supervision

The situation in South Africa mirrors the global move away from residential institutions. Fewer beds are available at ever-rising cost. Patients, their families and caregivers increasingly have to rely on their own resources. To help them in this task are the primary-care facilities, social clubs, seniors centres, daycare centres and respite-care facilities. Welfare organisations and non-profit organisations (NPOs) offering support, counselling and psycho-education are invaluable.

### 4.3 Pharmacological treatment

#### 4.3.1 Acetylcholinesterase inhibitors and memantine

Based on the cholinergic hypothesis of AD, cognitive deterioration is associated with progressive loss of cholinergic neurons and decreasing levels of acetylcholine in the brain. Both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) have been found to play an important role in the degradation of acetylcholine. Table 2 outlines these medications.

The 3 acetylcholinesterase inhibitors (AChEIs) differ in their pharmacological action: donepezil selectively inhibits AChE; rivastigmine affects both AChE and BuChE; and galantamine selectively inhibits AChE and also affects nicotinic receptors. To date, these differences have not been shown to result in differences in efficacy and tolerability.<sup>[20]</sup>

An alternative strategy is the inhibition of excitotoxic amino-acid neurotransmitters (e.g. glutamate, aspartate, homocysteine) which play an important role in the pathophysiology of dementia. Memantine is an N-methyl-D-aspartate receptor antagonist which regulates calcium flux across membranes and may protect against neuronal death.

A combination of an AChEI with memantine appears to be more effective than either agent on its own and is well tolerated, there being no pharmacokinetic or pharmacodynamic interactions between the two.<sup>[20,21]</sup>

Most indications for the above agents are AD-specific but may also benefit those AD patients with cerebrovascular disease. Other indications include MCI, diffuse Lewy body (DLB) dementia, and Parkinson's disease dementia. These indications are, however, country-specific as is their range of applications for the mild, moderate and severe stages of AD. The mode of administration (slow-release capsules, transdermal patches) further impacts more positively on tolerability,

**Table 2. Pharmacological treatment schedule for Alzheimer's disease<sup>[10]</sup>**

1. One of the following acetylcholinesterase inhibitors:
  - Donepezil (Aricept) 5 - 10 mg at night
  - Rivastigmine (Exelon) 3 - 6 mg twice daily
  - Galantamine (Reminyl) 16 - 24 mg daily
- and/or
2. NMDA receptor antagonist: Memantine (Ebixa) 10 - 20 mg daily.
3. Psychotropic agents for residual symptoms, i.e. mood (depression and irritability) and behavioural disturbances (restlessness, agitation, psychotic symptoms, insomnia).
4. Control of cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidaemia and smoking.

NMDA - N-methyl-D-aspartate

compliance and efficacy; as do ease of titration, price of product and familiarity with the medication. Under ideal circumstances, treatment should start in the prodromal/symptomatic/MCI phase of AD, bearing in mind that patients only tolerate the minimum effective dose in the early stages. The earlier diagnosis would involve the testing of cerebrospinal fluid biomarkers for AD, which is currently being standardised.<sup>[22]</sup> Patients respond with both improved cognitive and behavioural changes. Studies tend not to capture the more subtle changes in the dementing patient, such as the return of personality, spontaneity, insight and interest in their surroundings. The relief in caregiver stress burden is observed immediately, and this in turn enhances the well-being of the caregiver. Improvement in the mild to moderate AD patient is usually above baseline for the first 9 months; then it slowly declines as the illness relentlessly progresses. Data obtained at the 3-year mark show that patients are still functioning at above their expected level of deterioration when compared to untreated patients observed over the past decades.<sup>[23,24]</sup> With positive results, treatment may continue uninterrupted to an MMSE as low as 5/30, after which continuing benefit becomes increasingly questionable and difficult to evaluate in research;<sup>[17,25]</sup> or where the patient's dementia has progressed to a stage where there is no significant benefit from continued therapy.<sup>[26]</sup> Furthermore, longer-term follow-up data of AD patients on a previous generation AChE shows a cost-saving of 7.5% over the patient's lifetime from diagnosis to death.<sup>[27,28]</sup> Though the costs of medical and social services were reduced, most of the savings were due to reduced time in nursing home placement (at least 14 months). New treatments that can both improve clinical outcomes and save costs should be given serious consideration by clinicians and administrators.<sup>[29]</sup>

The benefits of treatment with AChEIs are rapidly lost when drug administration is interrupted for as little as 6 weeks and may not be fully regained when drug treatment is reinstated.<sup>[30]</sup> Notwithstanding, it may be necessary to check whether the medication is having the desired effect by very occasionally withholding treatment for approximately 2 weeks when the recurrence in severity of former NPS/behavioural and psychological symptoms of dementia (BPSD) target symptoms will act as an indicator for continued treatment.<sup>[26]</sup>

At least two-thirds of patients can be expected to derive modest benefit from the above medications with regard to not only improvement in cognition, but also to NPS/BPSD and activities of daily living (ADL). Failure to benefit from one AChEI or memantine does not necessarily mean that the patient will not respond to another of these medications.<sup>[19,20]</sup>

#### 4.3.1.1 Adverse effects

Excess cholinergic stimulation with the use of AChEIs may lead to transitory nausea, vomiting, dizziness, insomnia and diarrhoea. A lowering of dosage, short pause or even rechallenge (if treatment is re-initiated after a prolonged period) is usually successful in overcoming these events should they occur. Urinary incontinence, abdominal muscle cramps and excessive sweating may occur and usually indicate the need for a 'switch' to another agent. There appear to be no important differences between drugs in respect of type or frequency of adverse events.<sup>[20]</sup>

AChEIs may potentially have vagotonic effects on heart rate (i.e. bradycardia), of importance in patients with 'sick sinus syndrome'

or other supraventricular cardiac conduction disturbances such as sinoatrial or atrioventricular block. These medications should therefore be used with caution in patients with cardiovascular disease or those taking concurrent medicines that reduce heart rate. Bradycardic drugs include beta-blockers, digoxin, amiodarone and calcium channel antagonists. Recent reviews show that the incidence of cardiovascular side-effects is low and that serious adverse effects are rare. Interestingly, the value of pretreatment screening and routine electrocardiograms (ECG) is questionable and these are not currently recommended by the National Institute for Health and Clinical Excellence.<sup>[20,31]</sup>

Common (usually transient) side-effects of memantine include confusion, dizziness, headache and tiredness. Uncommon are anxiety, hypertonia and vomiting. Note that, being an amantadine derivative memantine may enhance the action of L-dopa and dopaminergic agonists.<sup>[20]</sup>

Generally, all the above interact with anticholinergic drugs and cholinomimetics to a variable extent.

#### 4.3.1.2 Recommended dosages

It is also important to optimise the dose and duration of cholinesterase inhibitor treatment. It is thought that the higher the dose tolerated by the patient, the better the result. A minimal trial period of between 3 and 6 months is indicated.

AD patients are given a once-daily dose of 5 mg donepezil at night, increasing to 10 mg after 4 weeks. Medication is given at night to obviate side-effects which may occur 4 hours after ingestion coinciding with peak plasma levels. The half-life of donepezil is 70 hours and steady state is usually obtained in 14 - 21 days. As with the other medications, should side-effects become intolerable, one skips the medication for a day or two.<sup>[20]</sup> Elimination of the drug is through both renal excretion of intact drug and bio-transformation via the cytochrome P450 system. The latter is only partially saturated by the drug, and hence drug-drug interactions tend not to be a problem. Rivastigmine is initiated at 1.5 mg twice daily, and increased by 1.5 mg twice daily every 2 - 4 weeks to a maximum of 12 mg daily. Rivastigmine has almost no potential for interaction since it is metabolised at the site of action and does not affect hepatic cytochromes. Galantamine is initiated at 8 mg daily, and the dose is then increased by 8 mg every 4 weeks to a maximum of 24 mg daily. Metabolism is via the cytochrome P450 system. Memantine is given in the morning with a starting dose of 5 mg, then raised in increments of 5 mg on a weekly basis to a maximum of 20 mg per day. Metabolism is primarily non-hepatic (Table 3).<sup>[10,20,32-34]</sup>

#### 4.3.1.3 Follow up

It is important to determine the patient's response to medication, and as such it may be useful to complete a scale such as the MMSE or ADL<sup>[15]</sup> or the Neuropsychiatric Inventory (NPI) for NPS<sup>[35]</sup> in order to help quantify the treatment response.

#### 4.3.1.4 Neuropsychiatric symptoms

NPS, also formally known as BPSD, rather than cognitive decline, prompt entry into long-term care. Over 90% of subjects with dementia will exhibit at least one NPS that needs specific management at some point in the course of their illness.<sup>[18,36]</sup> These symptoms may wax and

wane over time while some symptoms (e.g. visual hallucinations in DLB dementia) are more common in some dementias than in others. Another frequent mistake made by both caregivers and physicians alike is to assume that there are no hallucinations or delusions, since patients may objectively not display these phenomena which are only elicited on very careful mental state examination or behavioural assessment. The behavioural domains are best assessed by using the NPI.<sup>[35]</sup> The diffuse nature of the NPS means that each patient needs an individual assessment and treatment strategy.<sup>[18,32,35-37]</sup>

In general, once treatable medical causes for NPS have been addressed or eliminated, psychosocial intervention follows with or without psychotropic medication. The latter consists of the use of AChEIs or memantine on their own or in combination followed by antidepressant, antipsychotic or other medication as indicated.

The general treatment principles follow those for younger adults. Except that half to two-thirds of the adult dose is given. 'Start low, go slow, review frequently' is the standard watchword, as the elderly are more sensitive to medication side-effects than the younger adult. Note that polypharmacy may be necessary in the form of a non-sedating (high-potency) neuroleptic by day and a sedating (low-potency) neuroleptic at night. Psycho-education about the illness and supervision of medication is essential, keeping in mind that data on medication are, in general, controversial (Table 4).<sup>[32,36]</sup>

#### 4.3.2 Antidepressants

While symptoms of anxiety or depression are common in the premonitory stages of dementia, e.g. their occurrence at 50 years of age may herald dementia 10 - 20 years later, once the dementia is established, apathy is the most common NPS (frequently misinterpreted as 'depression').<sup>[18]</sup> Though major depression may precede the onset of AD, it occurs less frequently as the disease progresses, while minor depression, mild depressive symptoms or bouts of dysphoria become much more common in the early course of AD. If in doubt about the coexistence of depression with AD, a trial of antidepressant medication should be given. Note that antidepressants also have anxiolytic, and in the case of some newer-generation antidepressants, sedating if not hypnotic qualities. Symptomatic treatment of neuropsychiatric disturbances will afford both the patient and caregiver much relief. By and large the elderly require smaller dosages (about half to two-thirds) of antidepressant medication than that of the young adult population, and in most cases the 'sedating' antidepressants are preferred. Higher dosages may be required for more resistant cases where the diagnosis of coexistent depression is certain. Exercise caution with regard to side-effects and patient tolerance. AD patients with an MMSE of below 20/30 tend not to benefit from an antidepressant in terms of its antidepressant effect. AD patients on an AChEI, however, may experience depressive symptoms in both the mild and moderate stages of AD.<sup>[38]</sup> In these patients the depression appears in part to be coupled to the renewed insight afforded the patient by the drug, and is usually transient in nature. When it persists, treatment with an antidepressant is indicated.<sup>[38]</sup>

Avoid tricyclics in therapeutic doses on account of anticholinergic side-effects, and ECG QTc problems, especially when combined with other medication, e.g. antipsychotics.

Dementia patients fare better on 'sedating' antidepressants such as citalopram (20 mg), sertraline (50 - 150 mg), mirtazapine (15 - 30 mg)

**Table 3: Description of cognitive enhancers. Adapted from Taylor *et al.*,<sup>[32]</sup> Ihl *et al.*<sup>[33]</sup> and Rossiter<sup>[34]</sup>**

Name	Donepezil (Aricept)	Rivastigmine (Exelon)	Galantamin (Reminyl)	Memantine (Ebixa)
Derivative	Piperidine	Carbamate	Tertiary alkaloid	Amantidine
Therapeutic class	Acetylcholinesterase inhibitors	Acetylcholinesterase inhibitors	Acetylcholinesterase inhibitors	NMDA receptor antagonist
Therapeutic dose	5 - 10 mg at night	3 - 6 mg 2 x daily	16 - 24 mg daily	5 - 10 mg 2 x daily
Starting dose	5 mg at night	1.5 mg 2 x daily	8 mg daily	5 mg daily
Presentation	5 mg, 10 mg tablets	1.5 mg, 3 mg, 4.5 mg, 6 mg capsules	8 mg, 16 mg, 24 mg CR capsules	10 mg tablets/oral drops
Interval between dose increases	4 weeks	4 weeks	4 weeks	1 week weighted mornings
Common adverse effects (often transient)	Nausea, vomiting, diarrhoea, fatigue, insomnia, muscle cramps, anorexia, headache, vivid dreams	Nausea, vomiting, diarrhoea, dizziness, anorexia, confusion, headache, somnolence, muscle cramps	Nausea, vomiting, diarrhoea, abdominal pain, anorexia, fatigue, dizziness, headache, somnolence	Confusion, dizziness, headache, tiredness, constipation
Half-life (h)	70	12	7 - 8	60 - 100
Metabolism	CYP 2D6 CYP 3A4	Non-hepatic	CYP 2D6	Primarily non-hepatic
Drug-drug interactions	Yes	Interaction unlikely	Yes	Yes

NMDA = N-methyl-D-aspartate; CR = controlled release; CYP = cytochrome P.

**Table 4. Approach to neuropsychiatric symptoms/behavioural and psychological symptoms of dementia. Adapted from Ames *et al.*<sup>[36]</sup> and Taylor *et al.*<sup>[34]</sup>**

Take a routine history (patient and key informants) focusing on mental state (including MMSE) and assess interpersonal and environmental factors. Key questions around symptoms exhibited, the circumstances under which they arose and management strategies utilised to date.

Exclude physical illness potentially precipitating NPS/BPSD, e.g. constipation, infection (e.g. urinary tract infections especially from dehydration) and pain.

Target the symptom requiring treatment.

Consider non-pharmacological methods.

Psycho-educate the patient (if they have the capacity) and family/caregiver.

Carry out a risk/benefit analysis prior to selecting medication. Ideally start with an AChEI or memantine prior to other psychotropic medication. Discuss the use and side-effect profile fully with patient/family/caregiver.

Titrate medication from a low starting dose and maintain the lowest dose possible for the shortest period of time necessary.

Review medication regularly, monitoring for compliance, efficacy and adverse events.

Ensure support and ongoing psycho-education, monitoring and dealing with problems as they arise. Create awareness of local support group.

NPS = neuropsychiatric symptoms; BPSD = behavioural and psychological symptoms of dementia; AChEi = acetylcholinesterase inhibitors.

and agomelatine (25 - 50 mg) at night. Escitalopram (2.5 - 5 mg) and venlafaxine (75 - 225 mg) are given in the mornings. The latter should only be used as second-line treatment. Augmentation usually involves neuroleptics, while electroconvulsive therapy may only be effective during the prodromal phase of the disorder.

#### 4.3.3 Antipsychotics

Table 5 outlines a treatment schedule for restlessness, psychotic symptoms, agitation and insomnia. Note that haloperidol (a potent antipsychotic, with little sedation, but prone to extrapyramidal side-effects) acts synergistically with chlorpromazine (a less potent antipsychotic, sedating, and prone to postural hypotension as side-effect). The drugs in combination usually allow for a lower dose of

either agent, with fewer side-effects, affording better tolerability and targeting of symptoms. Some caregivers prefer one drug only, an even lower dosage of either agent, or different timing. Good caregivers will experiment with different regimens, tell you what their AD patient needs, and should be accommodated, for at the end of the day it is they who have to live with the consequences.<sup>[10,38]</sup>

When aggression, psychosis, resistance to care or restlessness is prominent, low-dose risperidone/haloperidol at 0.25/0.5 mg twice daily is the drug of choice. Reinforce the day-night cycle by adding a sedative antipsychotic such as quetiapine/chlorpromazine 25 - 50 mg at night (Table 5).<sup>[10]</sup> Titrate up as indicated. For acute sedation 1 - 2 mg lorazepam orally or intramuscularly is the drug of choice (Table 6).<sup>[10]</sup>



Ultimately, it is the treatment with which one is familiar and comfortable that works best. First-generation antipsychotics (FGAs) are probably as effective as second-generation antipsychotics (SGAs) but owing to their side-effect profile less well tolerated. As a rule of thumb, the ‘non-sedating’ antipsychotics have extrapyramidal symptoms as side-effects, the sedating antipsychotics have oversedation, hypotension and dizziness as their chief side-effect. There is no significant difference between treatment groups.<sup>[32,36]</sup>

In 2004 increased mortality with antipsychotics in dementia raised warnings for risperidone and olanzapine, which over the years were extended to include all SGAs as well as FGAs. The risk of developing both serious and non-serious cerebrovascular adverse events (CVAEs) such as stroke and mortality increases threefold with the use of antipsychotics. To date the mechanism by which the risk of such CVAEs is raised remains obscure, and patients with poorly controlled cardiac arrhythmias, hypertension, diabetes and previous stroke are more at risk.<sup>[32]</sup>

**4.3.4 Other medications/strategies**

**4.3.4.1 Hypnotics**

Avoid benzodiazepines on account of the frequent occurrences of daytime somnolence, emotional lability, confusion, incoordination, ataxia, memory impairment and incontinence. Implementation of measures of sleep hygiene is a prerequisite.

If medication is required for insomnia (preferably short-term) the following may be useful:

- Benzodiazepine-related: zolpidem 5 mg or zopiclone 3.75 – 7.5 mg
- Antidepressants: Sedating agents such as citalopram 10 - 20 mg, trazodone 50 mg, mirtazapine 7.5 - 15 mg or agomelatine 25 mg at night.

**Table 5. Example of a neuroleptic regimen<sup>[10]</sup>**

Haloperidol (Serenace)/risperidone (Risperdal) 0.5 mg/0.25 - 0.5 mg respectively twice daily.

Increase the dose to 0.75 mg, 1.0 mg and 1.5 mg twice daily, if necessary, for daytime control. Wait a day or two between increases.

*Together with:*

Chlorpromazine (Largactil)/quetiapine (Seroquel) 25 mg at night

Increase the dose to 50 mg, 75 mg and 100 mg at night, if necessary, for nocturnal control.

Wait a day or two between increases.

*Or:*

Olanzapine (Zyprexa) 2.5 - 5 mg at 17h00

**Table 6. Psychotropics for acute sedation<sup>[10]</sup>**

One of the following agents:

Lorazepam (Ativan)

1 - 2 mg po/IMI

0.5 - 1.5 mg IVI

Do not exceed 8 mg over 24 hours

Haloperidol (Serenace)

2.5 mg IMI/IVI

Do not exceed 10 mg over 24 hours

- Neuroleptics: Sedating agents such as chlorpromazine 25 mg, olanzapine 2.5 mg (given at 17h00) or quetiapine 25 mg at night.

**4.3.4.2 Mood stabilisers/anticonvulsants**

Trials with anticonvulsants (carbamazepine, sodium valproate, lamotrigine, topiramate and gabapentin) have not produced convincing evidence upon which to advocate their routine use.<sup>[32]</sup>

**4.3.4.3 Restless legs syndrome**

Clonazepam 0.5 mg may be taken at bedtime. Failing this, a dopamine agonist may be indicated: pramipexole, 0.125 mg at night.

**4.3.4.4 Hypersexuality**

Cyproterone acetate 150 mg given every 2 - 4 weeks IMI is effective in combating paraphilia in non-dementing patients and those with dementia. Sexual disinhibition or hypersexuality will diminish within a few days. The strategy is to administer the medication for 6 months, then withhold treatment, and should symptoms re-emerge, another 3 months of treatment is indicated. Very occasionally a further 3-month course may be necessary.<sup>[39]</sup>

**4.3.4.5 Treatment-resistant psychoses and disruptive vocalisers**

In these situations the clozapine/amisulpiride regimen (taking into account white cell count measurements) may be useful:

Initiate: clozapine

- Start with 12.5 mg (in very frail patients, prone to extrapyramidal side-effects)
- Increase in 12.5 mg increments
- Start with 25 mg (in more robust patients)
- Increase in 25 mg increments
- If response is good, continue to near-intolerance level
- Split dose with night-time weighting, then drop one level
- Total daily dose 125 - 300 mg
- Watch out for: sedation, hypotension, urinary incontinence and drooling

Add: amisulpiride

- Start with 50 mg
- Increase in 50 mg increments
- Split dose with night-time weighting
- Total daily dose 150 - 200 mg
- Watch out for sedation and dystonia

**4.4 Non-pharmacological treatment**

**4.4.1 The patient**

A complex interaction of biological, psychosocial and environmental factors contribute to the development of NPS in AD.<sup>[18]</sup> It is therefore important to observe for environmental triggers that influence behaviour, and get feedback from those around the patient. This has led to the A-B-C approach, whereby Antecedents to the behaviour are noted, as well as details of the Behaviour (description, time, duration), and the Consequences. A disruptive patient may thus get much more attention from nursing staff than when they are quiet, which inadvertently reinforces their disruptive behaviour.<sup>[18]</sup>

Environmental factors implicated in triggering NPS include excessive noise and stimulation, lack of daily structure and routine, confusing surroundings, excessive demands, loneliness and boredom.<sup>[18]</sup> Specific

non-pharmaceutical interventions that enjoy success are validation therapy, positive reinforcement, reminiscence therapy, reality orientation and creative diversions, among others.

#### 4.4.2 The caregiver

A most vital link in the pharmacotherapy and general care of AD is the caregiver. Caregivers are estimated to spend an average of 70 - 100 hours per week on providing care. Caregivers utilise 45% more physician visits and 70% more prescription drugs than non-caregivers, and are more likely to be hospitalised. More than 50% of caregivers are at risk for clinical depression.<sup>[40,41]</sup> A recent study<sup>[42]</sup> showed that, in general, there was a six-fold risk of dementia in spouses of patients with dementia. Where husbands looked after spouses suffering from dementia the risk was twelve-fold. Judicious use of pharmacotherapy, therefore, not only alleviates the stress on the caregiver but also delays the institutionalisation of the AD patient.

All caregivers should be referred to NPOs such as Dementia SA in the Western Cape and Alzheimer's South Africa, elsewhere. Not only do these organisations assist in supporting caregivers and monitoring their well-being but they also explain how to care for the patient, provide support services – such as home help or respite care – wherever possible, provide counselling and medicolegal advice, and continually update the caregiver by means of newsletters, meetings or workshops, on the latest developments.

#### 4.5 Preventative measures

It is estimated that the neurodegeneration in AD starts some 20 - 30 years before the appearance of the first clinical symptoms,<sup>[43]</sup> reflecting the need for earlier intervention while minimal brain damage has occurred.

Note that the preventative measures mentioned below offer no benefit to people whose preclinical AD pathology is sufficiently advanced to produce dementia symptoms within very few years and especially once the dementia is clinically evident:

- Hormone replacement therapy (oestrogen with or without progesterone) is only effective if initiated at the time of menopause where a deficiency in female sex hormones has clearly been established.<sup>[44]</sup>
- Vitamin E ( $\leq 400$  IU) and C (400 mg) daily, preferably in combination.<sup>[45]</sup> Note that high-dose vitamin E (+400 IU daily)

supplementation is associated with an increased mortality risk.<sup>[46]</sup>

- Red wine (Bordeaux blend 250 - 500 ml daily). Ascribed to resveratrol and other aliphatic compounds.<sup>[47]</sup>
- Non-steroidal anti-inflammatory drugs (NSAIDs). Conventional NSAIDs such as ibuprofen and voltaren<sup>[48]</sup> as well as naproxen used for as little as 2 - 3 years<sup>[49]</sup> may protect against AD.
- Coffee. Consuming 3 - 5 cups of coffee (not decaffeinated or instant) a day decreases the risk of dementia/AD later in life.<sup>[50-52]</sup>

Currently, there is interest in establishing a 'risk score' as early as midlife, similar to that of the risk of cardiovascular disease. It is hoped that these lifestyle changes, antioxidant supplementation and treatment of medical conditions may then decrease the risk of AD and other dementias in persons at risk.<sup>53</sup> A diet rich in vitamins B, C, D and E (fruit and vegetables) and omega 3

fatty acids (fish) and low in high trans-fat (processed foods) reflects in beneficial blood nutrient biomarker patterns influencing both cognitive function and brain volume.<sup>[54]</sup>

- Physical exercise
- Weight reduction
- Control of hypertension
- Control of hypercholesterolaemia
- Dietary antioxidants
- Intellectual activity
- Leisure activities and hobbies
- Social networks
- Red wine
- Fish and other sources of omega 3
- Folate-rich food or low-dose vitamin B supplementation

### 5. Algorithm

Fig. 3 shows the treatment algorithm for dementia.

For further reading on the biological treatment of AD, please refer to Ihl *et al.*,<sup>[33]</sup> Rossiter<sup>[34]</sup> and Daoud.<sup>[55]</sup>

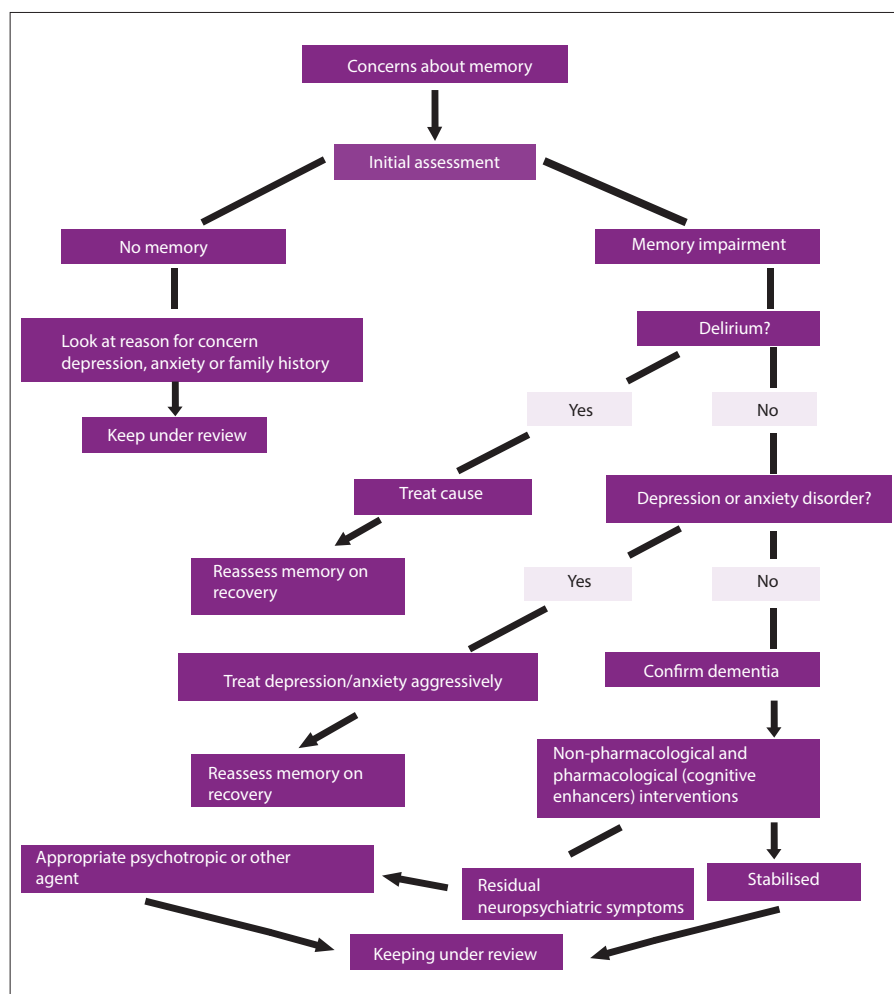


Fig. 3. Algorithm for therapy of dementia (adapted from Daoud<sup>[55]</sup>).

## 6. Summary points

- Treatment with antedementia medication combined with non-pharmacological measures provides the most benefits in patients with dementia.
- Medication must be individualised taking into account the constellation of symptoms, the stage of the disease, the side-effect profile, and caregiver availability.
- Titrate medication from a low starting dose.
- Target daily doses of first-line antedementia medication are as follows: donepezil 10 mg, rivastigmine 12 mg, galantamine 24 mg, and memantine 20 mg. This should, however, be guided by response and tolerability. These medications are effective in the symptomatic treatment of AD, VaD, DLB dementia, dementia in Parkinson's disease and certain frontotemporal dementias.
- Patients should be closely monitored for the first month after commencing treatment.
- The most promising approach to VaD is secondary prevention of CvD by addressing its risk factors.
- Rule out underlying or coexisting medical conditions and psychosocial environmental factors in patients with behavioural, mood or anxiety symptoms.
- In patients with depression, consider antidepressants that have more sedative effects, such as citalopram, sertraline, mirtazapine, and agomelatine. In view of the potential for QT prolongation, citalopram should not be used in doses greater than 20 mg per day in adults older than 60 years.
- For hyperactivity or agitation, a low-dose first- or second-generation antipsychotic medication may be used for a short period of time.

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