

CLINICAL PRACTICE GUIDELINES FOR MANAGEMENT OF DEMENTIA

STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subjected to change as scientific knowledge and technology advance and patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the health care provider in light of the clinical data presented by the patient and the diagnostic and treatment options available.

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Grading of recommendation:

The grading of recommendations of the types of evidence and grading of recommendations are set out in the following tables¹:

Level of evidence	
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb.	Evidence obtained from at least one other type of well-designed quasi experimental study.
III.	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV.	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

OR, the APA guidelines levels of confidence²:

Levels of confidence	
I.	Recommended with substantial clinical confidence
II.	Recommended with moderate clinical confidence
III.	May be recommended on the basis of individual circumstances.

Grade of recommendation	
A.	Required: at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation. [Evidence levels Ia, Ib] OR Level I clinical confidence
B.	Required: availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation. [Evidence levels IIa, IIb, III] OR Level II clinical confidence
C.	Required: evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. [Evidence level IV] Indicates absence of directly applicable clinical studies of good quality. OR Level III clinical confidence

SUMMARY OF RECOMMENDATION

Recommendation	Grade
General management principles	

Dementia is often progressive and symptoms will change over time. Similarly, treatment must evolved with time as new issues will emerged as symptoms change.	
At each stage the physician should be alert and help the patient and family anticipate future symptoms and care that may be required.	A
Psychiatric Aspects of Management	
The core treatment of a patient with dementia is psychiatric care which must be based on close alliance with the family/caregiver. A thorough psychiatric, neurological and general medical evaluation to determine the nature of deficits is required for every patient.	A
It is critical to identify and treat the general medical conditions that may contribute to the dementia and associated behavioural symptoms.	A
Ongoing assessment includes periodic monitoring of cognitive and non-cognitive psychiatric symptoms and their responses to intervention.	A
It is generally necessary to review patients on routine follow-up every 3-6 months.	B
More frequent visits may be required for patients with complex or potentially dangerous symptoms or during administration of specific therapies.	A
Safety measures need to be constantly reminded and evaluated.	A
Educating the patient and family about the illness, treatment, sources of care and support, and financial and legal issues is important.	A
NON-PHARMACOLOGICAL INTERVENTIONS	
Non-pharmacological interventions should always be considered along with drug options before treatment is started. Non- pharmacological management strategies in the management of dementia include behaviour -, stimulation - and emotion - oriented treatment approaches.	C
A care plan should be made for each individual.	

SUMMARY OF RECOMMENDATIONS³

Recommendations	Grade
NEUROLEPTIC DRUGS	
Neuroleptic drugs have been widely prescribed in the management of dementia but evidence for their efficacy is limited.	C
Patients should only be considered for treatment with neuroleptics if they have serious problems, especially psychosis, serious emotional distress or danger from behavioural disturbances.	
There is no clear evidence for the superiority of one neuroleptic over another. The choice depends on their side-effect profile.	C

Low doses should be prescribed initially with a slow and cautious increase, if necessary.	B
Treatment should normally be short term and should be reviewed regularly.	C
Awareness of potential side-effects including akathisia and tardive dyskinesia is important. The routine use of anticholinergics should be avoided.	B
Care should be taken to identify Lewy body dementia, because of the risk of severe side-effects.	
USE OF OTHER DRUGS	
Acetylcholinesterase inhibitors show modest efficacy in improving cognition in patients with mild to moderate Alzheimer's disease. This must only be used after a thorough discussion of their potential risks and benefits.	A
There is insufficient evidence at present to recommend the routine use of other cognitive enhancers such as vitamin E, selegiline, ginkgo biloba etc.	
Marked and persistent depression should be treated. Antidepressant medication may be used.	B
Severe and persistent anxiety may require short-term anxiolytic treatment.	C
Severe and persistent insomnia may require short-term hypnotic treatment.	C

Note :

All tables containing drug information are arranged in alphabetical order.

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1.0. INTRODUCTION:

Dementia is a syndrome in which progressive deterioration in intellectual abilities is so severe that it interferes with the person's usual social and occupational functioning. An estimated 5 to 10 percent of the adult population aged 65 years and older is affected by a dementing disorder. The prevalence doubles every 5 years among people in this age group⁴.

Despite its prevalence, dementia often goes unrecognised or misdiagnosed in its early stages. Many health care professionals mistakenly view the early symptoms of dementia as inevitable consequences of ageing. This clinical practice guidelines on the detection and management of dementia is targeted at healthcare professionals involved in the management of dementia.

2.0. DISEASE DESCRIPTION:

There are many definitions of dementia. The Royal College of Physicians defines dementia as the acquired global impairment of higher cortical functions including memory, the capacity to solve problems of day-to-day living, the performance of learned perceptuo-motor skills, the correct use of social skills, all aspects of language and communication and the control of emotional reaction, in the absence of clouding of consciousness. The condition is often progressive though not necessarily irreversible⁵.

As much of the research data on which recommendations are made is derived from the study of Alzheimer's disease, the recommendations made with regards to their management will apply to dementia in general. However dementia due to general medical conditions will not be covered in this guideline.

2.1. DIAGNOSIS:

2.1.1. The diagnosis of dementia can be made according to the DSM-IV classification⁶ as stated below or:

- A. The development of multiple cognitive deficits manifested by:-
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 and occupational functioning and represent a significant decline from a previous level of functional.

2.1.2. Based on the ICD classification⁷:

Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Consciousness is not clouded. Impairments of cognitive function are accompanied and occasionally preceded by deterioration in emotional control, social behaviour or motivation.

2.2. **Associated features** of dementia include behavioural and psychological symptoms. These symptoms can occur at any stage of the dementing illness.

The behavioural and psychological symptoms of dementia can be divided into 2 main groups:

2.2.1 **Behavioural problems** include:

2.2.1.1. Agitation

This can present as physical agitation including pacing, restlessness, disinhibited behaviour, wandering, stereotyping or verbal agitation such as complaining, requesting for attention, exhibiting negativism, repeated questioning or phrasing and screaming.

2.2.1.2. Aggression

Aggression can be physical such as hitting, pushing, tearing or crying, spitting, kicking, scratching and biting or verbal such as threats, accusations, name-calling or obscenities.

2.2.1.3 Apathy

Apathy is a common behavioural problem in AD and related dementias, and may occur even in the absence of depression⁸.

2.2.2. **Psychological presentations** of dementia include:

2.2.2.1. *Psychosis (hallucinations, misperceptions and delusions).*

2.2.2.2.. *Depression*

2.2.2.3.. *Others (insomnia and anxiety).*

2.2.3. Other **associated features** are changes in dietary habits and deficits in visuo-spatial functioning. The latter may lead them to underestimate risks involved in activities such as driving. Dementia is sometimes accompanied by motor disturbances such as gait disturbances, slurred speech and a variety of abnormal movements. Seizures and loss of sphincteric control can occur.

2.3. **TYPES OF DEMENTIA**⁷

Dementia can be categorised according to the various causes depending on pathology, clinical presentations and additional symptoms. The categories include:

290.xx. -- Dementia in Alzheimer's disease

290.xx.—Vascular dementia

294.1 .—Dementia due to....[indicate the general medical condition]

294.8 .—Dementia Not Otherwise Specified (NOS)

2.4. **DIFFERENTIAL DIAGNOSES:**

The differential diagnoses that need to be considered :

2.4.1. **Delirium**

Delirium is an acute confusional state. It may be superimposed on dementia as the underlying brain disease increases susceptibility to the effects of medication and medical illness. Delirium is characterised by a reduced ability to maintain attention, but unlike dementia, the cognitive deficits tend to fluctuate.

2.4.2. **Amnestic disorder**

This is also characterised by impairment in memory, but other cognitive domains remain intact.

2.4.3. **Age Associated Memory Impairment**

This is characterised by a mild decline in cognitive functioning occurring with ageing. However it is non progressive and does not lead to functional impairment.

2.4.4. **Mental Retardation**

This occurs before the age of 18, and is characterised by below average general intellectual functioning. Memory functioning may be intact.

2.4.5. **Schizophrenia**

In schizophrenia, the cognitive impairment tends to be less severe. The main established diagnostic criteria are that of perceptual and behavioural symptoms.

2.4.6. Major Depressive Disorder

This may be associated with complaints of memory impairment, difficulty in concentration and a reduced intellectual ability, sometimes referred to as pseudodementia. The course and onset of depressive symptoms as well as response to treatment may be the distinguishing features. However, as many as 50% of elderly patients with depression will go on to develop dementia⁹.

2.5. PREVALENCE AND INCIDENCE:

The prevalence of dementia show a consistent rate of about 5% in the age group 65 years and above for moderate and severe dementia¹⁰. The prevalence is found to increase exponentially with age so that the subgroup aged 65 years to 69 years is 1.5–2%, 75 to 79 year is 5.5-6.5% and 85 to 89 years is 20-22%¹¹.

There have been few incidence studies of dementia. Investigations generally reported an incidence of approximately 1% per year for the elderly¹².

There is relative excess of dementia of the Alzheimer's type [DAT] among women, and of vascular dementia among men.

2.6 COURSE AND PROGNOSIS

The mode of onset and subsequent course of dementia depend on the underlying aetiology. Dementia may be progressive, static or remitting. The reversibility of dementia depends on the underlying pathology, the availability and timely application of effective treatment.

The natural history of the disease is that of a decline due to progressive damage to widespread areas of the brain. As the overall functional status deteriorates, the person's ability to adjust to changes in the environment deteriorates to such an extent that death ensues. **Dementia shortens life expectancy; with estimates of median survival of 5 to 9.3 years**¹³.

2.7. STAGING OF DEMENTIA:

The level of decline in cognitive abilities leading to functional impairment is used to describe the stages and severity of dementia. The ability to perform a specific function depends on the baseline skills, deficits and the social environment. Dementia can be categorised as mild, moderate and severe. Detailed staging can be done using the Global Deterioration Scale or the Clinical Dementia Rating.

2.8. SPECIFIC DEMENTIAS:

*Dementia of the Alzheimer's Type or Alzheimer's disease accounts for 50 – 60% of all dementia cases. Vascular dementia can be seen in up to 15% of patients. Nineteen percent of patients have either Lewy body dementia or dementia associated with Parkinson's disease*¹⁴.

2.8.1. Dementia of the Alzheimer's Type:

This is a dementia of insidious onset and gradual progression. The onset of the illness occurs late in life, but rare and familial cases can present early (less than 50 years old). The most common early presentation is with deficits in recent memory. Sometimes deficits in executive function may occur. This is often followed by aphasia, apraxia and agnosia after several years. Psychotic symptoms are common in the middle and later stages. Motor signs occur late in the disease. The diagnosis should be made only when other aetiologies for dementia have been ruled out. A definitive diagnosis of Alzheimer's disease can only be made at autopsy, which reveals numerous

characteristic senile plaques and neurofibrillary tangles widely distributed in the cortex. Progression is gradual but steadily downward, with an average duration from onset of symptoms to death of 8–10 years.

2.8.2. Vascular Dementia

Typically vascular dementia is characterised by an abrupt onset and stepwise course in the context of cerebrovascular disease documented by history, focal neurological signs and/ or imaging studies. The pattern of cognitive deficits is patchy, depending on the regions of the brain affected. The onset of vascular dementia may occur at any time in life but becomes less common after the age of 75 years. The relationship between Alzheimer's disease and vascular dementia is a complex one. Strokes and Alzheimer's disease frequently coexist. Recent evidence suggests that small strokes can lead to increased clinical expression of Alzheimer's disease¹⁵. Vascular dementia can progress in a stepwise pattern but can be static. Early treatment of cardiovascular risk factors may prevent further progression.

2.8.3. Lewy body dementia

The main characteristics of Lewy body dementia are the presence of early and prominent visual hallucinations, fluctuations of symptoms and parkinsonian features. Patients are notably sensitive to the extrapyramidal effects of antipsychotic medication. It has a much more rapid evolution compared to Alzheimer's disease. Histopathologically, it is characterised by abundant Lewy inclusion bodies diffusely distributed in the cerebral cortex.

2.8.4. Dementia due to Parkinson's disease

Dementia is particularly common late in the course of Parkinson's disease. It is seen in 20–60% of patients with Parkinson's disease. The dementia in Parkinson's disease has an insidious onset and slow progression. It is characterised by cognitive and motor slowing, executive dysfunction and impairment in memory.

2.8.5. Frontal lobe dementias

Frontal Lobe Dementia and Pick's disease commonly occur in individuals between the ages of 50 and 60 years. Both are rare. The disorders are characterised by changes in personality, executive dysfunction, deterioration in social skills, emotional blunting, behavioural disinhibition and prominent language abnormalities. Difficulties in memory, apraxia and other features of dementia follow later in the course. Prominent primitive reflexes may be present. As the dementia progresses, apathy or extreme agitation may accompany. It may be difficult to assess cognitive impairment as individuals may develop severe problems with language, attention or behaviour. The course is progressive and tends to be more rapid than that of Alzheimer's disease.

2.8.6. Other dementias

There are a number of other disorders that can lead to progressive dementia such as Huntington's disease and Creutzfeldt-Jacob disease

3.0. ASSESSMENT OF A DEMENTED INDIVIDUAL:

3.1. PRINCIPLES:

A thorough psychiatric, neurological and general medical evaluation to determine the nature of the deficits is required for every patient [A].

3.1.1. Site of assessment:

The site of assessment is determined by the need to provide a safe environment in the least restrictive settings. The presence of familiar people helps to allay anxiety in the patient. Home assessment offers some advantages as the patient's daily activities and function can be assessed in familiar surroundings. Patients who are very frail or with significant medical illness or severe behavioural problems may require an inpatient facility^{16,17}

3.1.2. Frequency of assessment:

Ongoing assessment includes periodic monitoring of cognitive and non-cognitive psychiatric symptoms and their responses to intervention[A]. The frequency of visits is determined by a number of factors such as:

- Patient's clinical status and rate of functional decline
- Current treatment plan
- Need for specific monitoring of treatment effects
- Reliability of caregivers

Generally frequency of follow-up visits should at least be every 3 – 6 months[B]. More frequent visits are required for patients with more distressing symptoms or during administration of specific therapies[A].

3.1.3. Diagnostic evaluation:

Patients with dementia will require a thorough diagnostic evaluation [*see Appendix I*], in order to rule out irreversible or treatable cause of dementia. *Appendix II* shows the algorithm guiding the differential diagnosis of dementia.

An overview of a comprehensive assessment of people with dementia is outlined in the notes on good practise [*Appendix III and IV*].

The components of an assessment are:

3.2. CLINICAL ASSESSMENT:

3.2.1. The History:

The patient's premorbid state is the baseline from which all other information is judged. Background information is required for setting goals for therapy and rehabilitation.

3.2.1.1. The patient's history:

The patient's past memories can be informative especially regarding childhood experiences, family relationship, jobs, marriage and children. Remote memories and significant events can be maintained even in later stages of dementia.

3.2.1.2. The informant's history:

The patient's previous personality, attitudes, levels of activities, interests, social functioning and self-care can be obtained from a reliable relative. Information about the patient can also help to understand what new problems the family has to cope with.

3.2.2. Physical examination:

A full physical examination is necessary especially the central nervous system.

3.2.3. Mental and cognitive state examination:

The mental state examination incorporates appearance and general behaviour, mood, abnormal beliefs and abnormal experiences. Elicit any speech problem such as dysphasia and dysarthria.

Cognitive assessment includes attention, concentration, orientation, memory, intelligence and other cortical functions (visuo-spatial, visual agnosia, prosopagnosia, apraxia, topographical disorientation, right-left disorientation and finger agnosia).

3.2.4. Rating scales

The cognitive impairment can be quantified with the use of rating scales to measure intelligence and degree of impairment. The scales can be helpful in charting progress of the patient. Ratings can also be done on the behavior and activities of daily living.

The choice of any particular scale depends on the purpose of the assessment. A rating scale should not be regarded as an assessment on its own, but rather as a part of the assessment process. *Below are some scales that can be useful in the local context .[See appendix V for application of rating scales in different settings]*

3.2.4.1. Elderly Cognitive Assessment Questionnaire (ECAQ) – Kua et al.¹⁸:

This is a 10-item questionnaire assessing long-term memory, orientation and recall. A score of 7 or more is indicative of normal memory and a score of 4 and below indicate probable dementia. This is useful for routine screening.

3.2.4.2. Modified mini-mental state (MMSE) – Folstein et al.¹⁹:

This is the most widely used instrument for assessing severity of the dementia. However it can only assess the domains of cognitive deficit. The maximum score is 30. The lower the score, the more severely demented the patient is.

3.2.4.3. Clock drawing test

This is used as a measure of constructional apraxia and may also reflect frontal and temporoparietal functioning^{20,21}

3.2.4.4. Alzheimer's disease Assessment scales-cognitive (ADAS-Cog)²²

ADAS-cog provides an 11-item cognitive subscale assessing memory, language and praxis.

3.2.4.5. Scales for rating of severity

3.2.4.5.1. Global Deterioration Scale²³

This scale is used for staging of disease severity. The domains covered include the cognition, self-care and activities of daily living. It is clinician rated, based on information from patient and carer. It is rated from 1 to 7 points. A 7 point score indicates severe cognitive decline.

3.2.4.5.2. Clinical Dementia Rating²⁴

Six domains are assessed: memory; orientation; judgement and problem solving; community affairs; home and hobbies and personal care. The total CDR rating is the sum of boxes which presents an aggregate score for each individual's area.

3.2.4.6. Neuropsychiatric inventory²⁵

This scale evaluates a wide range of psychopathology and records severity and frequency separately. It assesses 10 behavioral disturbances, such as delusion, hallucination, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, apathy and aberrant motor behaviour.

3.2.4.7. Short Geriatric Depression Scale (SGDS) – Yesavage et al²⁶ :

A short 15-item questionnaire is used to assess the depression in dementia. The patient has possible depression if the score is 5 or more.

3.2.4.8. Activities of daily living (ADL):

ADL is an important component of the assessment of a demented patient. It refers to the personal and domestic tasks that form an integral part of the daily life. Assessment is the establishment of baseline information and identification of the patient's limitations and abilities.

Some of the instruments that can be used to assess function include *Instrumental Activities of Daily Living (IADL)*, *the Barthel Index* or *the Functional Activities Questionnaire (FAQ)*.

3.3. INVESTIGATIONS:

A diagnosis of dementia can be devastating to the patient and family. Hence ruling out other treatable causes of dementia should be a priority in the assessment of the patient.

3.3.1. Essential investigations

The investigations essential in the diagnostic work-up of the demented patient are as listed below, in Table 1.

Table 1:

Type of tests	
Blood	FBC & ESR Blood urea, creatinine and serum electrolytes Calcium Liver function test Thyroid function test Serum B12 and folate VDRL and TPHA
Urine	Urine FEME, culture and sensitivity
Radiologica 1	Chest X-ray

3.3.2. Optional investigations

If clinically indicated the following investigations may be required. (see Table 2.) :

Table 2:

	Type of tests
Neuroimaging	Brain CT Brain MRI
Electrophysiological	Electroencephalography
CSF studies	VDRL/TPHA
Others	HIV Heavy metals

3.3.2.1. Neuroimaging:

Not all patients with dementia will require neuroimaging. Neuroimaging is recommended in the following situations (adapted from the Canadian Consensus Conference in the Assessment of Dementia[CCCAD]1989²⁷)

- Age < 60 years.
- Use of anticoagulants and/or history of bleeding disorders.
- Recent head trauma.
- Previous history of carcinoma from sites that may metastasise to the brain.
- Unexplained neurological symptoms.
- Short duration of dementia (less than 2 years)
- Rapid unexplained decline (over 1 to 2 months)
- Localising signs.

- History of urinary incontinence and/or gait disorders early in the course of dementia.

4.0. MANAGEMENT OF DEMENTIA

The management of dementia would include:

- 4.1. General Principles of management
- 4.2. Non-pharmacological intervention
 - 4.2.1. General psychosocial intervention
 - 4.2.2. Specific psychotherapy/ psychosocial treatment
- 4.3. Pharmacological treatment

4.1. GENERAL PRINCIPLES OF MANAGEMENT:

The management of patients with dementia is multi-modal and is guided by the stage of the illness. It is also focused on the specific symptoms manifested by the patient. **At each stage the physician should be alert and help the patient and family anticipate future symptoms and care that may be required [A].**

The care of a demented patient requires an alliance with the family or caregivers [A]. The latter are an important source of information and are generally responsible for implementing and monitoring of treatment plans.

The management of patients with dementia is outlined in the flow chart {Appendix VI}.

A few general principles need to be applied in order for management to be effective in lessening distress and improving quality of life: -

4.1.1. Set reasonable goals.

Assess patient's deficits and change from the baseline functional level

4.1.2. Establish priorities.

Most patients have multiple problems. Treat the more distressing problems first. **Safety measures need to be constantly reminded and evaluated [A].**

The areas of concern are :

- 4.1.2.1. Evaluation of suicidal risk
- 4.1.2.2. Evaluation for potential violence
- 4.1.2.3. Recommendation regarding adequate supervision.
- 4.1.2.4. Prevention of falls.
- 4.1.2.5. Minimisation of hazards of wandering.
- 4.1.2.6. Vigilance regarding neglect or abuse.
- 4.1.2.7. Restriction of driving and use of dangerous equipment.

4.1.3. Decide who is to carry out the management.

A multi-disciplinary team is required. Choose a key member to work closely with patient and family.

4.1.3.1. Inform patient and caregiver of the illness.

4.1.4. Engage family members from the time of diagnosis.

Apart from caregiving, it is important to help patients and family plan for their financial and legal issues due to the patient's incapacity.

4.1.5. Set a time frame.

Plan ahead and set a date for reassessment. It is generally necessary to see the patient on follow-up visits every 3 – 6 months. Monitor the development of cognitive and non-cognitive psychiatric symptoms and their response to intervention.

4.1.6. Adequate documentation of patient’s medical records is important.

4.1.7. Assessing success or failure of the intervention

At review, the status of the problem should be reassessed. If goals are not reached, use different strategies and modify the management plan.

4.2. NON-PHARMACOLOGICAL INTERVENTIONS

The prolonged course of deterioration found in dementia takes a major emotional, psychiatric and physical toll among family members and caregivers. It is important to involve them early in the management²⁸. Resources must be made available to help patients and families cope with the condition and prepare them for the future.

Non-pharmacological intervention should always be considered along with drug option before treatment is started. Strategies include behavior, stimulation and emotion-oriented treatment approaches. A care plan should be made for each individual [C].

4.2.1. GENERAL PSYCHOSOCIAL INTERVENTION:

4.2.1.1. CARE PLAN

The psychosocial approach in the management of dementia should include an interdisciplinary care plan. An interim care plan should be generated immediately following assessment, and tailored to each individual patient.

Educating the patient and family about the illness, treatment, sources of care and support, and financial and legal issues are important component of the care plan [A].

The approaches are as follows²⁹:

- 4.2.1.1.1. Optimise function and quality of life.
- 4.2.1.1.2. Manage functional deficits.
- 4.2.1.1.3. Address psychosocial issues.
- 4.2.1.1.4. Address socially unacceptable/ disruptive behavioural symptoms
- 4.2.1.1.5. Address ethical issues.
- 4.2.1.1.6. Manage related complications or other existing conditions.

4.2..1.1.1. *Optimise function and quality of life.*

Patients with dementia often benefit from efforts to optimise their function and quality of life, independent of managing their problems. Excess disability may result from unrecognised or inadequately treated medical conditions, medications or various emotional, psychological and environmental factors. Excess disability will need to be prevented by:

- Identifying patient’s strengths and deficits
- Ensuring that appropriate assessments (vide supra) are done prior to initiating drug therapy.
- Monitoring for adverse reactions if drug therapy is initiated.
- Observing closely for possible symptom progression or general decline, which could be due to medications, progression of dementia or other medical complications.

4.2..1.1.2. *Manage functional deficits.*

- The healthcare provider and caregiver need to be aware of these deficits and maximise unimpaired functions. The approach should maintain dignity and the use of remaining capacities.
- The caregiver should assist the patient's ADL whilst avoiding negative reactions.

4.2.1.1.3. Address psychosocial and family issues.

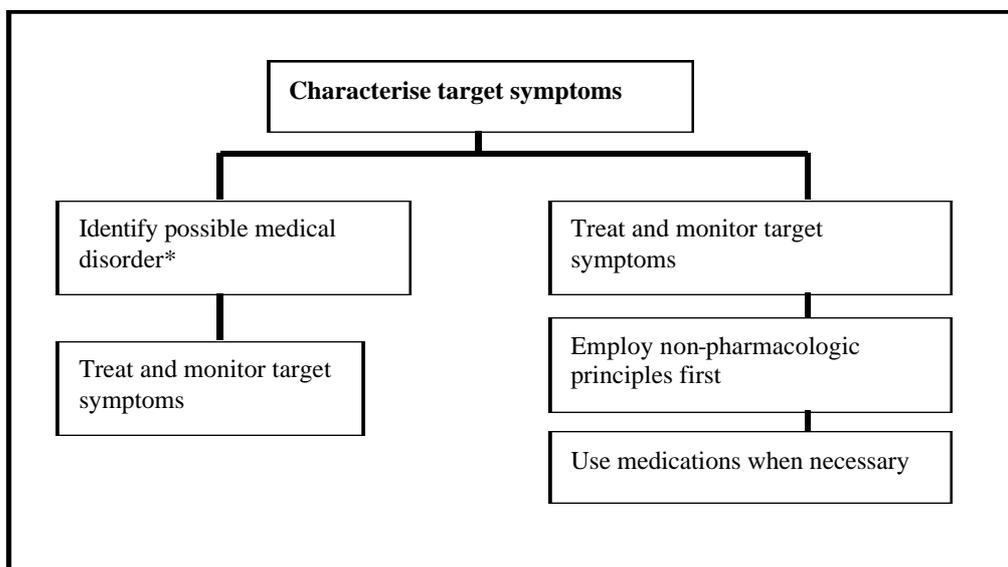
Pertinent psychosocial and family issues need to be addressed by:

- Working closely with families to help them understand the patient's diagnosis, impairments, management and prognosis³⁰.
- Using available resources such as the Alzheimer's Disease Foundation of Malaysia (ADFM). The ADFM has relevant publications and organises support groups.

4.2.1.1.4. Address socially unacceptable/ disruptive behavioural symptoms^{31,32}

- Environmental interventions should be tried first, while efforts are being made to identify causes, unless the behaviour symptoms potentially harm the patient or others.
- Pharmacological intervention if used initially, should be supplemented or replaced by other approaches.
- Disruptive behaviour may be reduced or eliminated by altering approaches to activities such as bathing, or environment to suit specific needs and/or concerns.
- The general approach to managing behavioural problems in dementia is shown in Fig.3.

Fig.3: General approaches to behavioural complications³²



*A useful mnemonic is **PAID**

- **P**HYSICAL PROBLEMS –e.g. infections
- **A**CTIVITY RELATED PROBLEMS – eg bathing
- **I**NTRINSIC DISEASE DETERIORATION
- **D**ELIRIUM AND DEPRESSION

It is critical to identify and treat general medical conditions that may contribute to the dementia and associated behavioral symptoms [A].

4.2..1.1.5. Address related ethical issues

- Define decision-making capacity³³ (healthcare providers need to be familiar with federal and state laws and statutes).
- Identify situations that require substitute decision-making e.g. giving consent.
- Address situations related to daily life – e.g. driving capacity, financial management.
- Medical and surgical interventions and/or end of life decisions – e.g. tube feeding, resuscitation.
- Whenever possible, involve the patient in decision-making, as even partial making capacity may suffice.

Specialist opinion may be required in some of the above situations.

4.2..1.1.6. Manage risks and complications related to dementia, other conditions or treatments.

- Anticipate risks and complications of treating dementia and be prepared to establish a plan to address them as they arise.

4.2.2.. SPECIFIC PSYCHOTHERAPIES/ PSYCHOSOCIAL TREATMENTS

Some patients may benefit from more specific psychosocial interventions. A review of the literature reveals modest efficacy of such treatments³⁴. The benefits that were shown do not usually persist beyond the duration of the intervention. Four major groups of psychosocial therapies are:

4.2.2.1 Behaviour oriented approach :

Behavioural approaches can reduce aggression, screaming and incontinence. A suggested approach is to establish:³⁵

- Description of the behaviour – where, when and how often it occurs.
- Assess specific antecedents and consequences of each problem.
- Alter or reduce activities that precipitate problematic behaviour.
- For complex activities, simplify or break into parts.

4.2.2.2 Emotion oriented approach :

This includes supportive psychotherapy³⁵, reminiscence therapy³⁶, validation therapy³⁷, sensory integration³⁸ and simulated presence therapy³⁹. Sensory integration has not been shown to be useful.³⁸ The others showed modest short-lived gains in mood, behaviour and cognition.

4.2.2.3. Cognition oriented approach :

This technique includes reality orientation⁴⁰ and skills training⁴¹. The aim is to redress cognitive deficits. Both techniques have shown transient benefits, but there have been reports of anger, frustration and depression⁴².

4.2.2.4. Stimulation oriented approach :

This treatment includes activities or recreational therapies [crafts, games and pets] and art therapies [music, dance, art]. They provide stimulation and help to mobilise patient's available resources⁴³.

4.3. PHARMACOLOGICAL INTERVENTIONS.

Drugs can be used synergistically with caregiver education to improve the management of the cognitive, functional and behavioural symptoms. There are special considerations that need to be taken into account.

- ‘Start low and go slow’
- Co-morbid medical problems
- Use of multiple medications, drug interactions & adverse effects.
- Development of instability, which leads to falls and injuries.
- Worsening of cognition.
-

Clinical trials in Alzheimer’s disease have focused on drugs that augment the levels of acetylcholine in the brain to compensate for losses of cholinergic function. The most successful to date have employed cholinesterase inhibitors⁴⁴⁻⁴⁸.

There are other agents considered in the treatment of AD. Research on these agents had not been as extensive as for the acetylcholinesterase inhibitors and hence not recommended for routine use.

4.3.0.1. Vitamin E and selegiline as monotherapy and not in combination, has been shown to be helpful in delaying the advent of poor functional outcome. The dosage of Vitamin E used in the trials was 2000 IU per day⁴⁹.

4.3.0.2. A randomised controlled trial using extract ginkgo biloba EGb 761 showed a small but significant benefit on cognitive measures in 309 pts with Alzheimer’s disease or vascular dementia. However, data on the non-cognitive and functional measures was inconsistent^{50,51}

4.3.0.2. The use of anti-inflammatory agents in dementia shows a reduced risk of Alzheimer’s disease only when it is used for more than 2 years.⁵²

4.3.0.4. Memantine, an N-methyl D-aspartate (NMDA) antagonist, has been found to be effective in the treatment of moderately severe to severe dementias including vascular dementia and HIV dementia. It has implication for use in other CNS disorders as well⁵³.

4.3.0.5. A single large trial on post-menopausal women using a selective estrogen-receptor modulator, raloxifene, did not improve cognition nor slow decline in post-menopausal women⁵⁴.

4.3.0.6. There is no evidence as yet for the routine use of piracetam⁵⁵.

4.3.0.7. There is some evidence of modest improvement in neuropsychological and behaviour measures with the use of ergaloid mesylate in vascular dementia^{56,57}.

4.3.1. For cognitive improvement

4.3.1.1. Cholinesterase Inhibitors:

There are several compounds of cholinesterase inhibitors. Drugs currently available in Malaysia are donepezil (benzylpiperidine compound), rivastigmine (carbamate compound) and galantamine (phenatrene alkaloids compound). Trials so far had shown modest efficacy for these agents³⁵⁻³⁹.

Use of acetylcholinesterase inhibitors must only be used after a thorough discussion of their potential risks and benefits [A].

In clinical practice, it is the prescriber’s responsibility to make a detailed assessment and diagnosis.

Table 3: Summary of recommendations for use of cholinesterase inhibitors ⁵⁸⁻⁵⁹.

Entry for drug treatment	<ol style="list-style-type: none"> 1. McKhann's criteria of probable AD⁶⁰ 2. Duration > 6 months 3. MMSE¹³: >12 4. Global and behavioural functioning and activities of daily living must be assessed before prescription. 5. Global Deterioration Scale²³ (GDS) score < 6-7. 6. Compliance must be assured. 7. Good family support. 8. Non-institutionalised patients.
Three phase evaluation of response	<ol style="list-style-type: none"> 1. Early: 2 – 4 weeks for adverse effects 2. Later: Assessed between 2-4 months for: <ol style="list-style-type: none"> a. MMSE b. Evidence of global or behavioural improvement 3. Review 6 monthly. Continue treatment only while MMSE remains >12.
Stop treatment	<ol style="list-style-type: none"> 1. Early if poor tolerance or compliance 2. If drug is no longer effective : <ol style="list-style-type: none"> a. <i>early</i> - continued deterioration at pre-treatment rate after 3 – 6 months. b. <i>late</i> - accelerated deterioration occurs after a period of maintenance treatment (after excluding PAID) c. * Drug-free period suggest drug no longer helping.
* Recommence treatment	If drug-free period (within 6 weeks) leads to deterioration.

Preliminary evidence indicate that these agents may have value in other dementias, such as dementia with Lewy bodies^{61,62} and vascular dementia⁶³.

Table 4: Recommended dosages for cholinesterase inhibitors

Compound name	Daily dose (mg)	Dosing
Donapezil	5 – 10	Once daily
Galantamine	16 – 24	Bid
Rivastigmine	6 – 12	Bid

Adverse effects and drug interaction:

Adverse effects include nausea and vomiting, muscle cramps, fatigue, insomnia, bradycardia and dizziness. In general adverse effects tend to wane within 2 to 4 days of treatment. Caution is required with the following medications due to potential interactions. (Table 5)[See **APPENDIX VI**]⁶⁴.

4.3.2. For behavioural and psychological symptoms of dementia (BPSD)

4.3.2.1. Treatment for psychosis and agitation

The frequency of psychotic symptoms varies between 30-50%.⁶⁵ Intervention for psychosis should be guided by the level of distress and risk to the patient and/or caregiver. Reassurance and distraction may be all that is required if distress or danger is small. **Psychopharmacological treatment is indicated if the distress puts the patient or caregiver in danger [C].**

The priority in treating distress or agitation is a careful medical evaluation (See Fig 3). Agitation may result from an occult medical condition, undetected pain, depression, insomnia or delirium. Treatment of the underlying condition often reduces the agitation. The next step is to assess the patient's overall situation. Physical discomfort, interpersonal issues or emotional difficulty could present as agitation. Behavioural measures need to be instituted before deciding on psychopharmacologic intervention. Other measures include hospitalisation and one-on-one care.

Once pharmacological intervention has been initiated, its continued use must be regularly evaluated and justified.

4.4.2.1.1. Antipsychotics

Neuroleptic drugs have been widely prescribed in the management of dementia, even though evidence for their efficacy is limited [C].

There is no clear evidence for the superiority of one neuroleptic over another. The choice depends on their side effects profile [C].

Conventional neuroleptics are effective in the management of BPSD^{66,67}. High potency agents (e.g. haloperidol, trifluoperazine) are more strongly associated with extrapyramidal symptoms and akathisia, whilst the lower potency agents (eg. chlorpromazine, thioridazine) can cause excessive sedation, delirium, and postural hypotension. Thioridazine has been associated with risk of prolonged QT⁶⁸.

Awareness of potential side-effects including akathisia and tardive dyskinesia is important [B].

The incidence of tardive dyskinesia with conventional neuroleptic treatment is 30% per year⁶⁹.

Treatment should normally be short term and time-limited (i.e. 8 – 12 weeks), and reviewed regularly [B]. Long-term exposure to conventional antipsychotics can cause deterioration of the dementing illness⁷⁰. **Routine use of anticholinergics should be avoided [B].**

The atypical antipsychotic agents are associated with fewer side effects⁶⁷.

Table 6: Guidelines for antipsychotic medication dosages

Class/ generic	Dose Equivalent	Initial dose (mg/d)	Typical range (mg/d)
Phenothiazine			
Trifluoperazine	2	1 - 2	2 – 10
Butyrophenones			
Haloperidol	1.5	0.25 – 0.5	0.5 – 5
Dibenzodiazepine			
Clozapine	100	6.25 – 12.5	25 – 100
Quetiapine	-	12.5 - 25	75 – 125
Benzisoxole			
Risperidone	0.5	0.25 – 0.5	1 – 2.0
Thiobenzodiazepine			
Olanzapine	-	2.5 - 5	5 – 15

Patients with Diffuse Lewy Body Dementia (DLB) can develop severe and fatal sensitivity to conventional neuroleptics⁷¹. **Care should be taken to identify dementia with Lewy Body, because of the risk of severe side-effects [B].** So very low doses of the atypical antipsychotics can be used with careful monitoring, for emergence of symptoms of neuroleptic sensitivity.

4.4.2.0.2. Benzodiazepines

Symptoms that respond best to benzodiazepines include anxiety, tension, irritability and insomnia. Trials have shown that benzodiazepines perform consistently better than placebo, but not as well as antipsychotics^{72,73}.

4.4.2.0.3. Antiepileptic Drugs

Carbamazepine and sodium valproate have been used in the treatment of agitated patients with dementia^{74,75}. A therapeutic trial of either of these agents may be used for nonpsychotic patients or in those who are sensitive or not responsive to antipsychotics.

Table 7: Recommended dose for anticonvulsant treatment in agitated patient

Class/ generic	Initiating dose	Therapeutic range (mg/d)	Therapeutic blood level (ng/l)*
Carbamazepine	100 mg bd	300 - 1800	8 – 12
Sodium valproate	200 mg bd	400 - 2400	50 – 100

*Therapeutic monitoring may be indicated in situations where compliance or toxicity is suspected

4.4.2.1. Treatment for depression

Depression can occur in up to 10-50% of patients with dementia⁶⁵. Contributing factors such as comorbid medical conditions, substance abuse and medications, need to be evaluated. **Marked and persistent depression should be treated. Antidepressant medication may be used [B].**

Severe depression with neurovegetative signs and suicidal ideation may need electroconvulsive therapy (refer ECT guidelines). Unilateral ECT is preferable as it reduces the risk of cognitive side effects⁷⁶. The cognitive component in demented patients with depression does not respond to antidepressants

The treatment of apathy may overlap those for depression. Dopaminergic agents, including psychostimulants, have been used for the treatment of apathy and of depressed elderly individuals with severe general medical disorders⁷⁷.

4.4.2.1.1. Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs) are recommended as first line treatment. When prescribing SSRIs, physicians need to be aware of their many drug interactions and adverse effects such as nausea and vomiting, akathisia, parkinsonism, sexual dysfunction and weight loss.

Tricyclic agents need to be used with caution and only for patients who are adequately supervised due to their cardiovascular side effects and anticholinergic properties. Imipramine and amitriptyline are agents with more prominent anticholinergic activity. The recommended dosages for initiating and maintenance of antidepressant treatment are outlined in Table 8.

Table 8: Recommendation for antidepressant dosing⁷⁸

Class/ generic	Starting dose (mg/d)	Daily dose (mg/d)
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SSRI		
Citalopram	10	20
Fluvoxamine	50 - 100	50 – 300
Fluoxetine	20	20 - 40
Paroxetine	20	40
Sertraline	25-50	25-200
RIMA		
Moclobemide	150 - 300	300 – 600
5HT2 receptor blockade		
Nefazodone	200	200 – 400
Alpha-2 antagonist		
Mirtazapine	15	15 – 45
NSRI		
Venlafaxine	75	75 – 150
Tetracyclic		
Maprotiline	25 – 50	25 – 150
Mianserin	10 - 30	30 – 90
Tricyclic		
Dothiepin	25	25 – 150
Clomipramine	10	30 – 50

4.4.2.2 Treatment for anxiety

Severe and persistent anxiety may require treatment with benzodiazepines[C]. Short-acting benzodiazepines are preferred and effective for short periods of 4 to 6 weeks. The long-term efficacy of these drugs has not been well studied. The side effects of excessive sedation, ataxia, delirium, paradoxical anxiety and respiratory depression may limit their use.

4.4.2.3. Treatment of sleep disturbance

Sleep disturbances are common in dementia. Pharmacological treatment should only be initiated if sleep hygiene and behavioural measures have been unsuccessful.

If insomnia is severe and persistent, short term hypnotic treatment may be required [C]. In pharmacological agents with short to medium half-lives and few metabolites are to be favoured⁷⁹ [Table 9].

Table 9: Guidelines for use of sedative-hypnotics in dementia.

Drug	Dose range
Chloral hydrate	1 – 2gm
Lorazepam	0.5 – 1.0mg
Midazolam	3.75 – 15mg
Zopiclone	3.75 – 7.5 mg
Zolpidem	5.0 – 10.0mg

Caution : Benzodiazepines can be habit forming

5.0. FACTORS MODIFYING TREATMENT DECISIONS

The treatment of dementia varies through the course of the illness, as symptoms evolve over time. A variety of factors may affect symptomatology, which can modify treatment decisions. Physicians should be vigilant for cognitive and non-cognitive symptoms that are likely to be present and take necessary action. In the early stages of the illness the patient and family should always be reminded to plan for the future (see Treatment of Patients and their Families).

5.0.1. COMORBID CONDITIONS

5.0.1.1. General medical conditions

Chronic general conditions commonly coexist with dementia. The memory impairment and disabilities associated with dementia will hamper the patient's ability to provide a reliable description of symptoms. Family and caregivers involvement is essential in evaluation.

5.0.1.2. Delirium

Patients with dementia are at a much higher risk of developing delirium. Among the common causes of delirium in demented individuals include the presence of general medical conditions, neurological disorders and drugs, including all psychotropic medications.

To diminish the prevalence and morbidity of delirium :

- avoid unnecessary medications,
- use the lowest effective doses of drugs,
- recognise changes from baseline behaviour and
- treat underlying causes.

5.0.1.3. Parkinson's disease

Dementia coexisting with Parkinson's disease requires a different treatment approach. The dopaminergic agents may predispose to the development of visual hallucinations and other psychotic symptoms. The minimal dose needed to control the motor symptoms should be used. If the psychotic symptoms result in distress or danger, antipsychotic

treatment should be used judiciously. The use of atypical antipsychotic agents is favoured. Clozapine has been best studied to date. Patients with Parkinson's disease may have coexisting depression, which can be misdiagnosed as dementia. A careful evaluation is required.

5.0.1.4. *Stroke*

Patients with a history of stroke, irrespective of whether it contributes to dementia, need to be evaluated to determine the aetiology of the stroke. Control of vascular risk factors, including the use of antiplatelet agents/anticoagulants as prophylaxis may be appropriate.

5.0.2. SITE SPECIFIC ISSUES

The care of patients with dementia should also be adapted to his/ her environment. Certain issues arise more frequently in particular care settings.

5.0.2.1. *Home*

The majority of the demented individuals are cared for in their own residence. Carers of patients with dementia often face psychological distress. Depressive disorders occur in 30% of spousal caregivers and ranges from 22% to 37% in adult children. **Home aids, daycare and respite services can provide relief to both patient and family.**

5.0.2.2. *Daycare*

Daycare can be one of the options whereby caregivers can get a break to attend to other responsibilities during part of the day. It offers a protected environment and provides appropriate stimulation to the patient. Activities must, however, be selected with care according to the patient's level of severity.

5.0.2.3. *Long term care*

As the severity of the illness progresses, a proportion of patients will eventually require placement in long-term care. These facilities should be tailored to meet the needs of the patients, especially to adequately address behavioural symptoms. Factors that need to be looked into include:

- knowledge of nursing home staff about dementia
- structured activity programmes that can improve behaviour and mood
- privacy
- maximising of daily functional activities
- medications
- use of restraints

5.0.2.4. *Inpatient general medical and surgical services*

Patients admitted may be at risk of developing problems which can lead to aggression, wandering, climbing over bed railings, removal of intravenous lines and refusal of medical procedures. The 3 main possibilities and their intervention are summarised below [Table 10].

Table 10: Common causes of behavioural problems in an inpatient service and suggested intervention

Causes	Intervention
Cognitive impairment leading to lack of comprehension and lack of memory of what had been told.	<ol style="list-style-type: none"> 1. Encourage familiar person to stay with patient. 2. Frequent orientation and explanation of procedures and plans 3. Adequate lighting. 4. Avoidance of overstimulation.
Development of delirium	<ol style="list-style-type: none"> 1. Elimination of unnecessary medications. 2. Attention to fluid and electrolytes status.

	3. Prompt treatment of underlying infection.
	4. Pharmacological management
Problems in communicating needs.	Thorough evaluation to identify an occult medical problem or possible source of discomfort.

5.0.2.5. General psychiatric inpatient units

At times the treatment of psychotic, affective or behavioural symptoms may warrant admission into an inpatient psychiatric units, where both non-pharmacologic and pharmacologic treatment can be more intensive.

5.0.3. DEMOGRAPHIC AND SOCIAL FACTORS

5.0.3.1. Age

Age is an issue in management as most individuals with dementia are old and frail. They have multiple general medical problems that will lead to more difficult diagnosis and treatment, and much greater disability. Dementia occurring in middle age is more likely to have more devastating effects on patients' lives and coping.

5.0.3.2. Gender

Dementia affects the female gender more often. Women are more likely to outlive their spouse. Caregivers will most likely be their adult children who often have jobs outside the home and have their own family to attend to. This may contribute to their earlier institutionalisation.

5.0.3.3. Family history

Some forms of dementia, such as Alzheimer's disease may have a genetic basis, with the identification of genes on chromosome 21, 14 and 1 in early-onset AD and presence of APOE-4 in late-onset AD. Currently, there is no evidence that screening for such genes confers any benefit. It may be appropriate to provide counseling to the family.

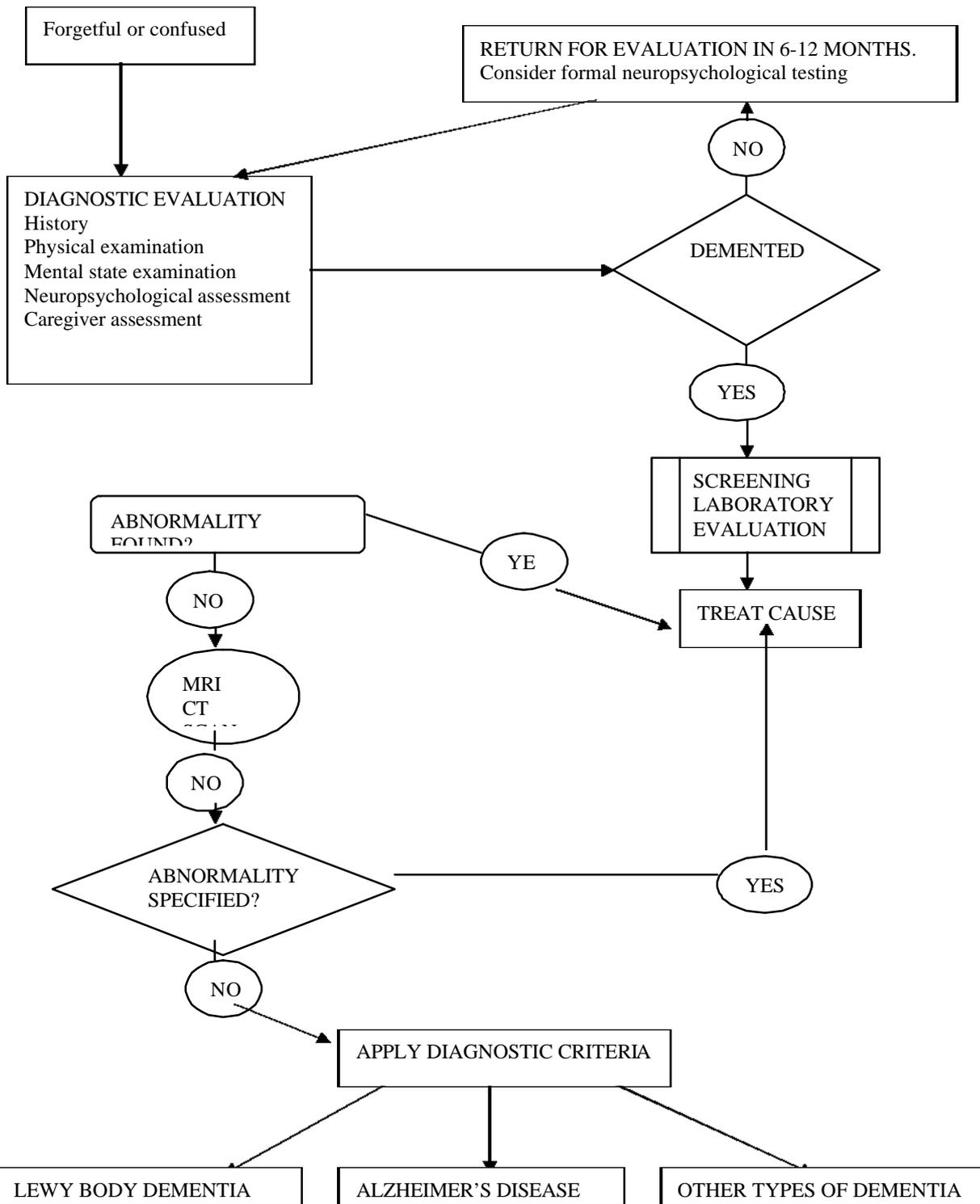
5.0.3.4. Others

Other factors to consider are :

- network of friends, neighbours and community
- availability of local resources
- local support services
- financial support
- ethnicity (this can have an impact on care giving style, symptom presentation and tolerability of behavioral problems)

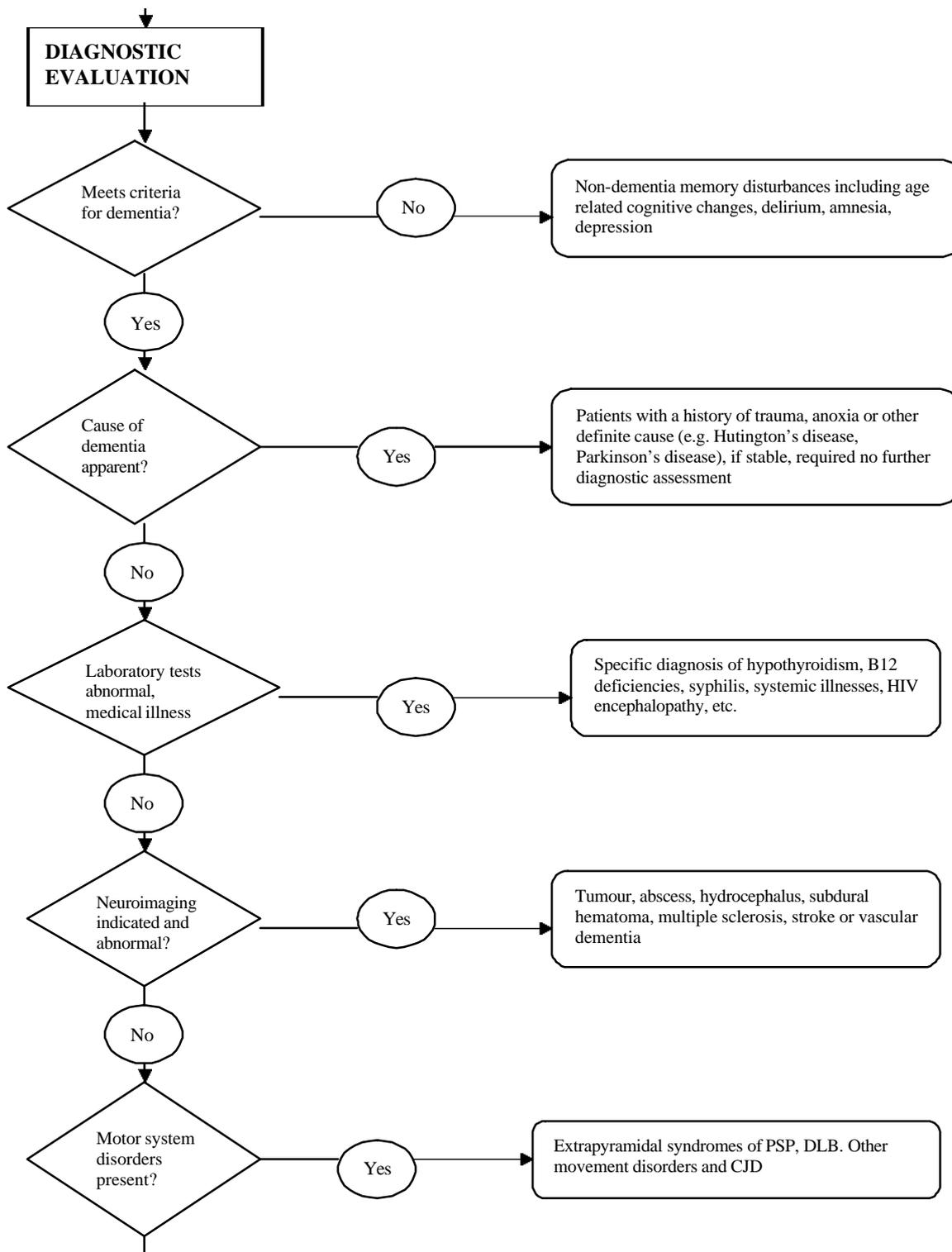
6. RESOURCE MATERIALS

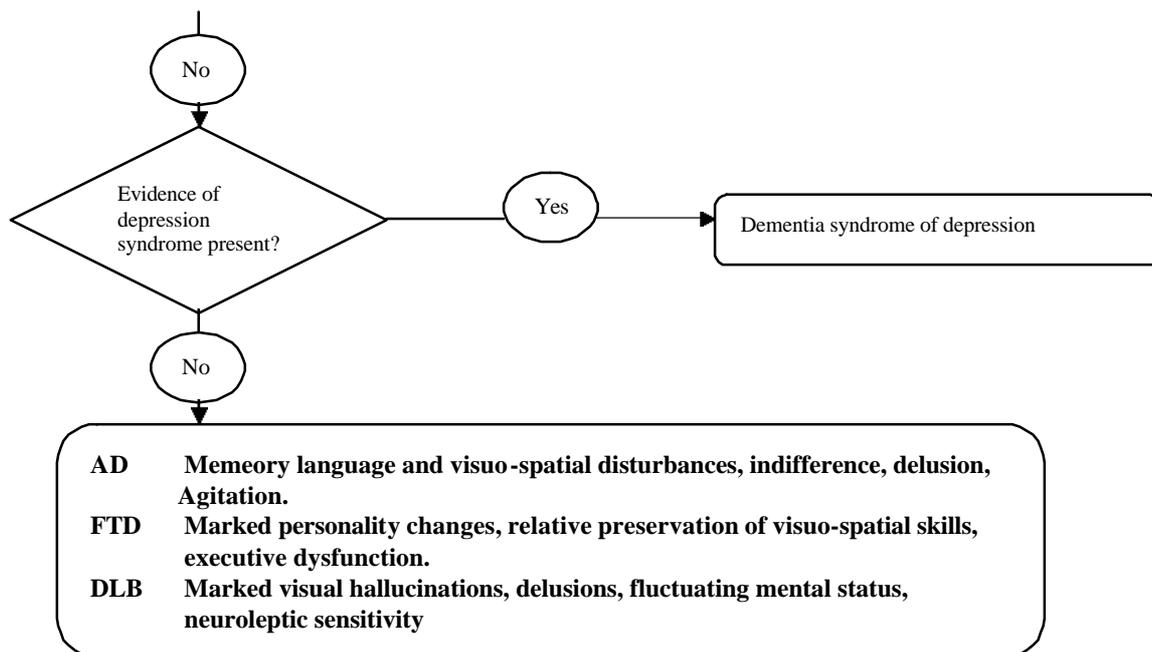
APPENDIX I.	Algorithm on diagnostic evaluation
APPENDIX II.	Algorithm guiding differential diagnosis
APPENDIX III.	Notes on good clinical practise
APPENDIX IV.	Notes on good clinical practice
APPENDIX V.	Management algorithm
APPENDIX V.	Suggested rating scales
APPENDIX VI.	Potential drug interactions



APPENDIX II: ALGORITHMS GUIDING THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA⁸¹

Memory complaint or decline in other cognitive function





Notes on good practice in the assessment of people with dementia³.

6.1. GENERAL ASSESSMENT

6.1.1. A **global approach** is required in the assessment which should embrace the patient's:

- Psychological state
- Physiological condition
- Social status
- Lifestyle, life history, needs and preferences.

Much of the assessment process can be undertaken by trained non-medical staff.

6.1.2. Details are required of **current medical status**, including:

- Medical history
- Current state of health
- Current medication

6.1.3. The **needs of informal carers** are particularly important.

6.1.4. **Current functional status** is also important and a review of lifestyle and ability to carry out activities of daily living to establish needs and required support services is essential.

6.1.5. **Standardised assessment procedures** are recommended, with routine use of simple tests of:

- Disorientation
- Memory tests
- Attention and concentration
- Other features of cognitive function such as aphasia, apraxia and agnosia
- Mood
- Activities of daily living

These can and should be assessed and consideration should be given to the patient's previous life history.

APPENDIX IV.

Notes on good practise.....continued

6.2. BEHAVIOUR

Behaviour is a complex phenomenon, and may have multiple causes. Accurate assessment of behaviour which is perceived as a problem is crucial in identifying the most likely causes, hence contributing to the focus of intervention and increasing the chances of its success.

Multi-causal model of behaviour.

An assessment should consider the following factors:

6.2.1. Person with dementia

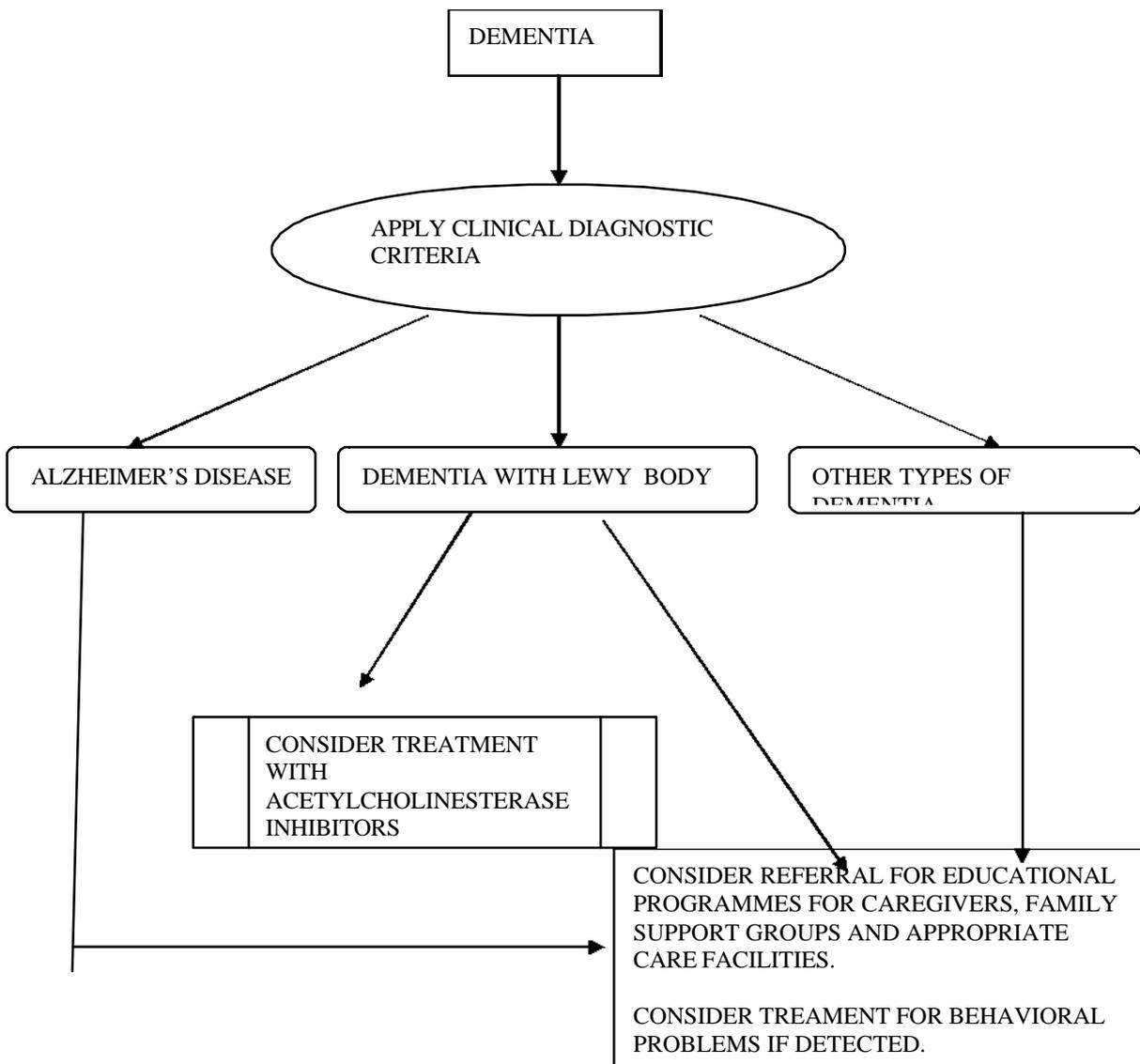
- Premorbid personality, including coping mechanisms
- Premorbid relationship with carers
- Nature and extent of impairment
- Physical/ medical problems, including medication, nutrition, alcohol consumption.
- Emotional reactions to losses, frustrations, life events, etc.
- Depression/ anxiety etc.
- Non-cognitive aspects of dementia.

6.2.2. Environment

- Change, e.g from home to resident
- Over/ understimulation
- Lack of privacy
- Lighting
- Noise
- Deprivation of dignity and individual rights
- Smoking

6.2.3. Caregivers

- Relationship to person with dementia
- Attitudes and coping mechanisms
- Approach to caring
- Knowledge of dementia
- Emotional reactions
- Physical and mental health.



APPENDIX VI

Table 11: Suggested rating scales to be used for assessing person with dementia and cognitive impairment

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Clinical issue	When to use	Where to use	What to use
Cognitive impairment	Screening	GP	ECAQ MMSE CDT
		Medical	MMSE CDT
		Nursing home	MMSE
Dementia	General profile	Specialist setting & Memory clinic	MMSE ADAS-cog CDT Verbal fluency Ischaemic scores
	Global ratings Staging BPSD ADL		GDS/ CDR GDS/ CDR NPI FAQ Blessed Dementia scale Barthel Index

APPENDIX VII.

Table 5.: Potential interactions of cholinesterase inhibitors⁵³

Interacting drugs		Side effects
Cholinomimetics		Potential
Muscarinic agonists		Bronchospasm
Phenothiazines TCAs Antihistamines		Reversal of action
H2 receptor blockers	Ranitidine	Potential
	Cimetidine	Prolong neuromuscular block during anaesthesia ↑ GI motility Muscle weakness
Metoclopramide		↑ GI motility
Succinylcholine		Potential
Beta-blockers		Bradycardia
Antiasthmatics (BRONCHODILATORS)		Bronchospasm

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