CLINICAL PRACTICE GUIDELINES

November 2009

MOH/P/PAK/196.09(GU)

Management of DEMENTIA

(2nd Edition)

Forget-me-not

MINISTRY OF HEALTH MALAYSIA

MALAYSIAN PSYCHIATRIC ASSOCIATION

ACADEMY OF MEDICINE MALAYSIA

MALAYSIAN SOCIETY OF NEUROSCIENCES
persatuan neurosains malaysia

This guideline is intended a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

This guideline was issued in 2009 and will be reviewed in 2012 or sooner if new evidence becomes available

CPG Secretariat
Health Technology Assessment Section
Medical Development Division
Ministry of Health Malaysia
4th floor, Block E1, Parcel E
62590, Putrajaya.

Electronic version available on the following website
www.moh.gov.my
www.acadmed.org.my
www.psychiatry-malaysia.org
www.neuro.org.my

Images on the cover

i) Dr. Aloysius "Alois" Alzheimer was credited with identifying the first published case of "presenile dementia", which would later be known as Alzheimer's disease.

ii) Myosotis laxa is a species of forget-me-not flower which is used as an emblem for the Alzheirmer disease association in some countries.

GUIDELINE DEVELOPMENT

The development group for these guidelines comprised of family medicine specialists, geriatricians, psychiatrists, geriatric psychiatrists, a neurologist, a psychologist, a public health specialist, an occupational therapist, a scientific officer and pharmacists from the Ministry of Health and the Ministry of Higher Education, Malaysia. During the process of development of these guidelines, there was active involvement of a review committee from both the public and private sector, consisting of geriatricians, psychiatrists, occupational therapist, neurologists and a representative from the caregivers group.

This document is the 2nd Edition of Clinical Practice Guideline (CPG) on the Management of Dementia updating the previous CPG on Management of Dementia (2003). Since the publication of the first guidelines, there have been many advances in the field of dementia and mild cognitive impairment. There is a movement towards very early detection of dementia with the development of genetic, neuroimaging and biomarkers. Acetylcholinesterase inhibitors (AChEI) have been around for the past twenty years for the treatment of Alzheimer disease and related dementias. Currently there has been another drug developed to treat severe dementia. There are also many more drugs undergoing Phase II and III trials that are targetting beyond the neurotransmitters. Drugs and other preventive measures, such as exercise and mental stimulation, have been investigated to determine the extent of risk that these factors have in the development of dementia.

This CPG was adapted from DEMENTIA, A NICE –SCIE Guideline on Supporting People with Dementia and their Cares in Health and Social Care, the British Psychological Society & Royal College of Psychiatrists, 2006 and the Scottish Intercollegiate Guidelines Network, Management of Patients with Dementia, February 2006. These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) tool prior to adaptation. Further evidence was then retrieved from 2006 onwards. For the purposes of updating these guidelines, June 2009 should be considered the starting point for searching for new evidence.

Literature search was carried out at the following electronic databases, PUBMED/ MEDLINE, PsycINFO, Cochrane Database of Systemic Reviews (CDSR), International Health Technology Assessment Websites, Journal full text via the OVID search engine, Database of Abstracts of Reviews of Effectiveness; Cochrane Controlled Trials Registered, Clinical Trial and Registry, EBSCO search engine. A snowball method was used to manually check the references of the included studies to identify any relevant studies that had not yet been included. Refer to Appendix 1 for the search terms used to retrieve articles.

Reference was also made to other guidelines such as the Ministry of Health Singapore - Clinical Practice Guideline, Dementia, 2006 and the Royal Australian College of General Practitioners, Care of Patients with Dementia in General Practice, September 2003.

The clinical questions were divided into four subgroups and members of the development group were assigned individual clinical question within these subgroups. The group members met a total of 25 times throughout the development of the guidelines. All literature retrieved were appraised by at least two members, presented in the form of evidence tables and discussed during group meetings. All the statements and recommendations formulated were agreed upon by both the development group and review committee. Where the evidence was insufficient, the recommendations were derived by consensus of the development group and review committee. This CPG is based largely on the findings of systematic reviews and meta-analyses in the literature, taking into consideration local practices.

These articles were graded using U.S. Preventive Services Task Force while the grading of recommendation in this guideline was modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network (SIGN). Refer to inside back cover for Levels of Evidence and Grade of Recommendations.

The draft guideline was posted on the Ministry of Health Malaysia and Family Medicine Specialist websites for comment and feedback. These guidelines had also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVE

GENERAL OBJECTIVES

The aim of these guidelines is to assist clinicians in making evidence based decisions on the management of people with dementia and their caregivers.

SPECIFIC OBJECTIVES

- ☑ To describe the syndrome of dementia and its common subtypes as well as mild cognitive impairment
- ☑ To discuss risk factors and preventive strategies in the development of dementia
- ☑ To review the assessment and diagnostic tools in dementia
- ☑ To provide evidence based guidance on the management for people with dementia and mild cognitive impairment
- ☑ To address the ethical issues and end-of-life issues in dementia
- ☑ To understand the impact of dementia on the individual and caregiver

CLINICAL QUESTIONS

Refer to Appendix 2 for details

TARGET POPULATION

a. Inclusion Criteria (Target Group)

Adults with dementia and mild cognitive impairment

b. Exclusion criteria

People with learning disabilities who develop dementia and dementia secondary to medical conditions e.g. normal pressure hydrocephalus, AIDS, dementia complex, etc.

TARGET USERS

These guidelines are applicable to healthcare professionals who are involved in the management of dementia:-

- ☑ Primary Care Physicians
- ☑ Psychiatrist/Geriatric Psychiatrist/Neuropsychiatrist
- ☑ Physicians/Geriatricians/Neurologists
- ☑ Nurses
- ☑ Social Workers
- ☑ Physiotherapists/Occupational Therapists
- ☑ Pharmacists
- ☑ Psychologists
- ☑ And all others involved in the management of patients with dementia

HEALTH CARE SETTINGS

Outpatient, inpatient and community setting

PROPOSED CLINICAL AUDIT INDICATORS FOR QUALITY MANAGEMENT

Indicator

Percentage of people with a possible diagnosis of dementia from primary clinic referred to memory clinics/specialist clinic =

$$\frac{\text{Total number of those suspected dementia who are referred from primary care to memory clinic}}{\text{Total number of referrals for suspected dementia in the memory clinic}} \times 100\%$$

Percentage of patients with BPSD prescribed atypical antipsychotics =

$$\frac{\text{Number of patients with BPSD prescribed atypical antipsychotics appropriately}}{\text{Total number of BPSD cases}} \times 100\%$$

GUIDELINE DEVELOPMENT GROUP

Chairperson

Dr. Suraya Yusoff
Head of Department and Senior Consultant Geriatric Psychiatrist
Hospital Sultan Ismail
Johor

Members (alphabetical order)

Dr. Bharathi Vengadasalam
Geriatric Psychiatrist and Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia, Serdang, Selangor

Ms Hor Yee Yee
Pharmacist
Hospital Sultan Ismail
Johor

Dr. Ismail Drahman
Head of Department and Senior Consultant
Geriatric Psychiatrist
Hospital Umum Sarawak. Sarawak

Dr. Khairuddin A. Wahab
Consultant Psychiatrist
Hospital Permai, Johor Bharu
Johor

Dr. Joseph Ngeh
Consultant Geriatrician
Hospital Umum Sarawak, Sarawak

Dr. Lee Fatt Soon
Senior Consultant Geriatrician
Hospital Kuala Lumpur
Kuala Lumpur

Ms. Mariammah Krishnasamy
Scientific Officer (Microbiology)
Health Technology Assessment Section
Medical Development Division, MOH

Dr. Mohd Daud Che Yusof
Family Medicine Specialist
Klinik Kesihatan Sungai Mati,Muar, Johor

Dr. Norhashim Ahmad
Consultant Neuropsychiatrist
Hospital Sultanah Aminah, Johor Bharu

A/Prof Normah Che Din
Clinical Psychologist and Lecturer
Faculty of Allied Health Sciences
Universiti Kebangsaan Malaysia
Kuala Lumpur

Dr. Norzarina Md Zabidi
Clinical Psychiatrist
Hospital Melaka
Melaka

Dr. Shanti Viswanathan
Neurologist
Neurology Department
Hospital Kuala Lumpur, Kuala Lumpur

Dr Sheamini Sivasampu
Public Health Physician
Health Technology Assessment Section
Medical Development Division, MOH

Dr. Sukumar Rajaretnam
Family Medicine Specialist
Poliklinik Komuniti Tanglin, Kuala Lumpur

Mr.Tan Chee Chin
Pharmacist
Hospital Sultanah Aminah, Johor Bharu
Johor

Mr.Thillainathan Krishnan
Occupational Therapist
Hospital Selayang
Selangor

Dr. Yau Weng Keong
Senior Consultant Geriatrician
Hospital Kuala Lumpur, Kuala Lumpur

REVIEW COMMITTEE

The draft guideline was reviewed by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence supporting the recommendations in the guidelines.

Chairperson

Professor Dr. Phillip Poi Jun Hua
Senior Consultant Geriatrician
Universiti Malaya Medical Centre
Kuala Lumpur

Members (alphabetical order)

Dr. Chin Ai-Vyrn
Consultant Geriatrician and Senior Lecturer
Universiti Malaya Medical Centre
Kuala Lumpur

Dr. Esther Ebenezer
Consultant Geriatric Psychiatrist and Lecturer
Universiti KL Royal Medical College Ipoh
Perak

Prof Dr. Goh Khean Jin
Senior Consultant Neurologist
Universiti Malaya Medical Centre
Kuala Lumpur

Prof Dr. Raymond Azman Ali
Deputy Dean and Senior Consultant Neurologist
Universiti Kebangsaan Malaysia Medical Centre
Kuala Lumpur

Associate Prof (Clinical) Dr. Rosdinom Razali
Consultant Psychiatrist and Geriatric Psychiatrist
Universiti Kebangsaan Malaysia Medical Centre
Kuala Lumpur

Datin Dr. Rugayah Bakri
Deputy Director
Health Technology Assessment Section
Medical Development Division, MOH

Dato' Dr. Suarn Singh
Head of Services for Psychiatry and
Senior Consultant Psychiatrist
Hospital Bahagia Ulu Kinta, Perak

Puan Tan Foo Lan
Head of Department
Department of Occupational Therapy
Hospital Kuala Lumpur

Dr. Yen Teck Hoe
President
Malaysian Psychiatrist Association
Hospital Tung Shin
Kuala Lumpur

Datuk Dr. Yim Khai Kee
Chairman of the Executive Committee
Alzheimer Disease Foundation Malaysia
Kuala Lumpur

EXTERNAL REVIEWERS

The draft guideline was also reviewed by a panel of external reviewers

Professor Helen Chiu
Professor & Head of the Department of Psychiatry
Chinese University of Hong Kong
Hong Kong

Professor Dr Khoo Ee Ming
Department of Primary Care Medicine
University of Malaya
Kuala Lumpur

Professor Leon Flicker
Professor & Geriatric Medicine Director
Western Australia Centre for Health & Ageing
University of Western Australia
Royal Perth Hospital

Dr. Mohd Faudzi Abdullah
Family Medicine Specialist
Klinik Kesihatan Padang Serai
Kulim, Kedah

Dr. Mohmad bin Salleh
Public Health Specialist
Family Health Development Division
Ministry of Health

Madam Pushpamani Navaratinarajah
Nursing Tutor
Nursing School, Seremban ,
Negeri Sembilan

Professor Rachelle Doody
Effie Marie Cain Chair in Alzheimers Disease
Research Dept of Neurology and Alzheimers
Disease and Memory Disorder Centre Baylor
College of Medicine, Houston, Texas

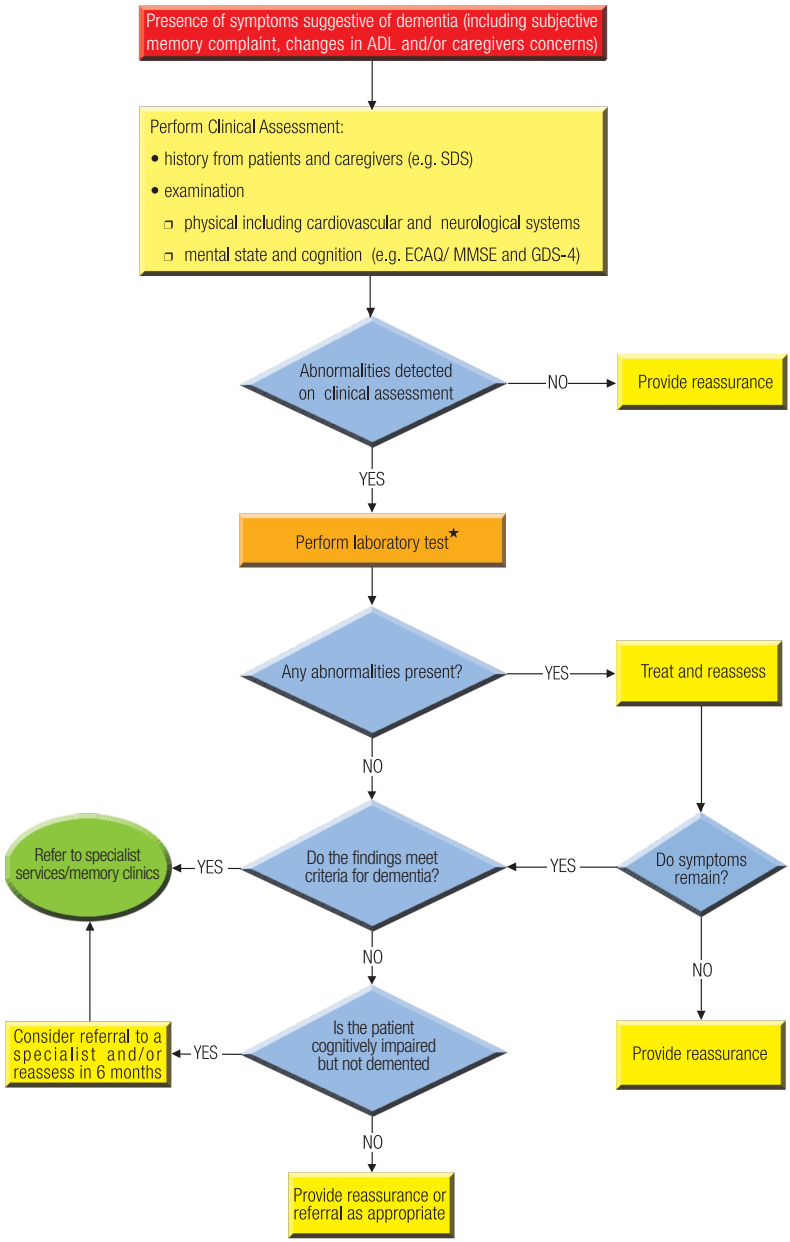
Datuk Dr. Raihanah Abd Khalid
Consultant Neurologist
Assunta Hospital
Selangor

Dr. P. Srinivas
Consultant Geriatrician/Chest Physician
Gleneagles Medical Centre Penang
Penang

Dr. Theva Raj Ponnudurai
Head of Services for Rehabilitation Medicine &
Senior Consultant Rehabilitation Specialist
Hospital Tuanku Jaafar, Seremban, Negeri Sembilan

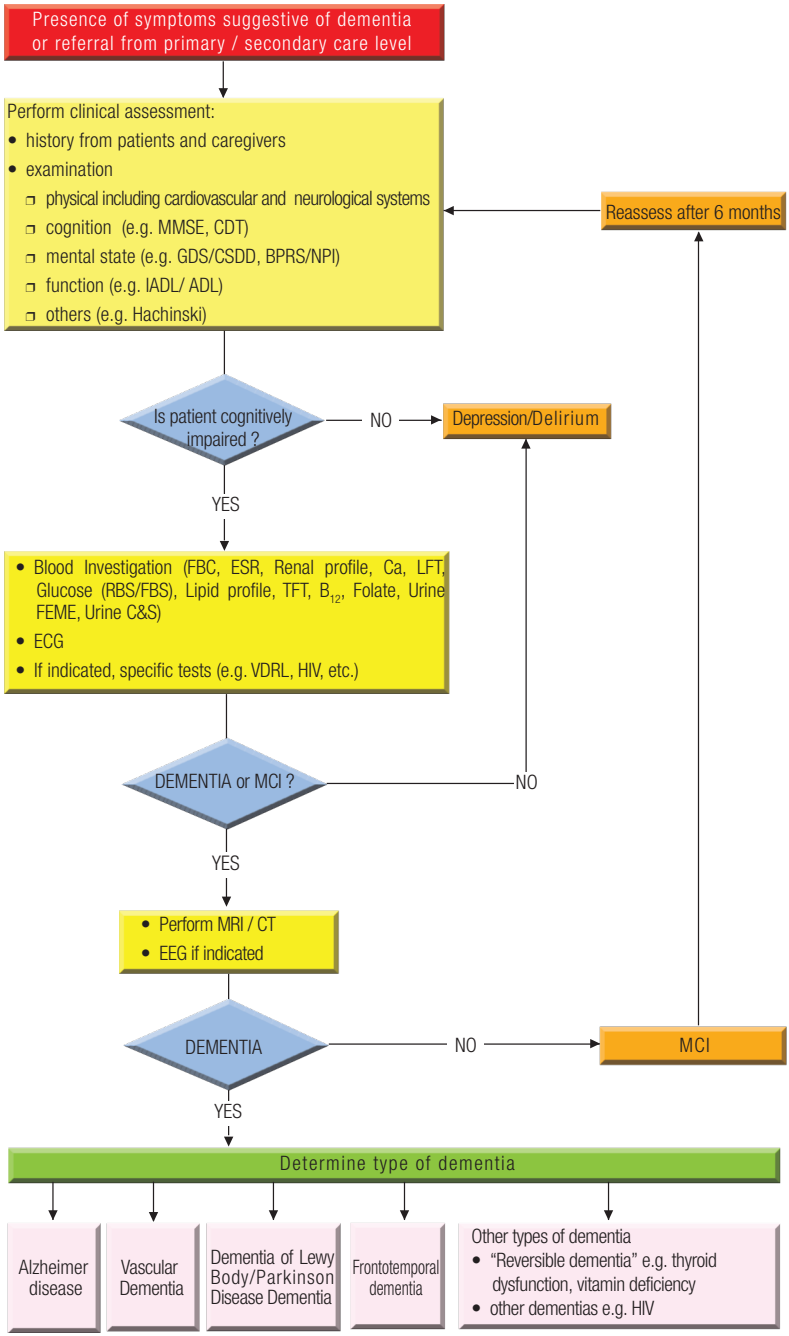
Dr. Yoong Kar Yaw
Head of Department and
Senior Consultant Physician
Hospital Sultan Ismail
Johor

ALGORITHM ON SCREENING OF DEMENTIA IN PRIMARY CARE

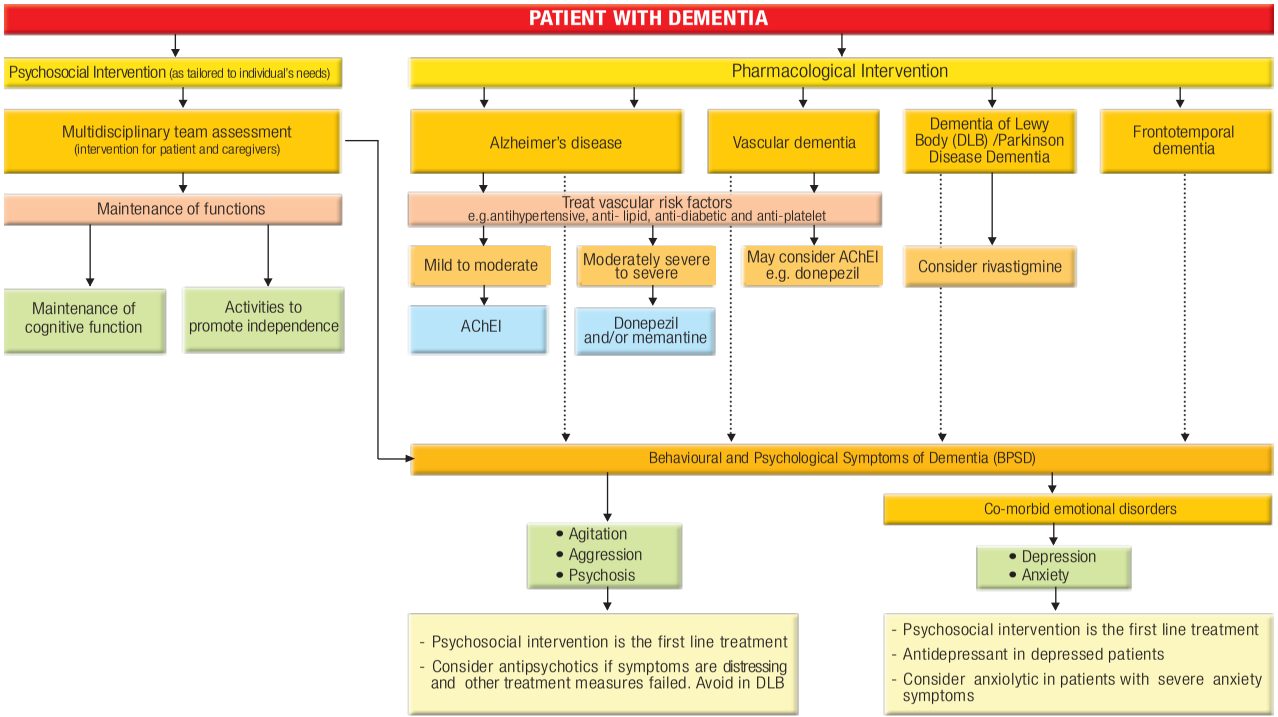


- ★Screening tests : FBC, Renal profile,Ca, LFT, Folate, B12,TFT, UFEME, RBS/FBS, Lipid profile.
- Specific test guided by clinical presentation : VDRL, HIV, etc.

ALGORITHM FOR DIAGNOSIS OF DEMENTIA AT SECONDARY/TERTIARY LEVEL



ALGORITHM FOR MANAGEMENT OF DEMENTIA



LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

TABLE OF CONTENTS

1.0 INTRODUCTION

Dementia is a syndrome characterised by diverse behavioural, cognitive and emotional impairments. The Royal College of Physicians of London, defined dementia as an acquired global impairment of higher cortical functions including memory, capacity to solve problems, learned percepto-motor skills, social skills, language and communication, and control of emotion, in the absence of clouding of consciousness. [1] The associated features of dementia include behaviouraland psychological symptoms. These symptoms can occur at any stage of the illness, and may be the most likely reason for people with dementia (PWD) being brought for medical attention. The condition is progressive though not necessarily irreversible. It has been reported that 15% of people with dementia have a potentially treatable cause, but the prevalence of reversible dementia is only 1%.[2],[3]

1.1 INCIDENCE AND PREVALENCE

It is estimated that there are 24.3 million people with dementia worldwide, with 4.6 million new cases each year. The number of people affected is expected to double every 20 years. The forecasted rate of increase is estimated to be more than 300% in India, China and their South Asian and Western Pacific neighbours. About 6.1% of the population 65 years of age and older, suffer from dementia (about 0.5% of the worldwide population). Fifty nine percent of PWD are females. [4],[5]

There have been few prevalence studies of dementia in Malaysia. A community survey (n=223) amongst Malays aged 60 years and above in Selangor, found that 24% were cognitively impaired.[6] Another study (n=522) found the prevalence of dementia in an urban community of Malays (aged 60 years and above) in Kuala Lumpur was 6%.[7] A large community study of the elderly in Malaysia (n=2980, aged 60 years and above) yielded a prevalence of organic mental disorder (inclusive of dementia) at 14.4%. [8] Among those living in the government residential homes, the prevalence of probable dementia are higher, at 36.5%.[9]

In the United States Health Retirement Study (HRS), the prevalence of AD, VaD and all dementia increased with age, reaching 37.4% dementia prevalence among individuals aged 90 and older. [10]

1.2 GENERAL CLINICAL FEATURES

The symptoms of dementia may be divided into two major groups-the cognitive and non-cognitive symptoms.

The **cognitive symptoms** comprise of memory impairment especially learning of new material, which is the most prominent early symptom. Previously learned material may be lost in more severe dementia. Language may also be affected. Individuals may have difficulty with spatial tasks, such as navigating around the house or in the immediate neighborhood. Poor judgment and poor insight are also common. These cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previous level of functioning. The order of onset and relative prominence of the cognitive disturbances and associated symptoms vary with the specific type of dementia.

The **non-cognitive symptoms** encompass the neuropsychiatric symptoms (NPS) or the behavioural psychological symptoms of dementia (BPSD). The behavioural component includes verbal or physical agitation, aggressive and non-aggressive behavior which can be verbal or physical, such as wandering, disinhibition, sundowning syndrome, and others. The most common psychological symptoms are depression, sleep disturbances, and psychotic symptoms (delusions of persecution and misidentification, and hallucinations). Anxiety is fairly common, and some patients manifest "catastrophic reactions," an overwhelming emotional responses to relatively minor stressors such as changes in routine or environment. Dementia is sometimes accompanied by motor disturbances, which may include gait difficulties, slurred speech, and a variety of abnormal movements. Other neurological symptoms, such as myoclonus and seizures, may also occur.

1.3 SUBTYPES

The clinical diagnoses of dementia rely mostly on recognizing patterns of neurological and cognitive impairment, rather than on specific biomarkers or other laboratory approaches. Diagnostic problems arise because the neurological findings are usually non-specific, and the cognitive profiles may overlap.

1.3.1 Alzheimers disease

Alzheimers disease (AD) remains the most common type of the primary degenerative dementia, accounting for 60-80% of cases. [11] It is characterised by progressive deterioration of short term memory and other higher cortical functions. Motor skills are generally preserved until late in the disease. Supportive features include altered behaviour and inability to carry out activities of daily living (ADL). It predominantly affects the older age group (> 65 years), but early onset can occur. A clinical diagnosis of AD can be made accurately in 90% of cases, but diagnosis can only be confirmed on brain biopsy by the presence of neuritic plaques (NPs), which are the accumulated deposits of amyloid B_{40} and amyloid B_{42}, and neurofibrillary tangles (NFTs), the hyperphosphorylated tau proteins. The severity of the cognitive decline is more closely related to the NFTs burden. It is yet unknown what triggers the changes in the neurons.

1.3.2 Vascular Dementia

The term vascular cognitive impairment covers a broad range of cognitive deficits from mild impairment to dementia, that can be associated with vascular factors. [331] However, in this guideline, the focus will be limited to only vascular dementia.

Vascular dementia (VaD) is a heterogeneous disease with diverse vascular pathologies, such as strategic infarcts, multiple cortical infarcts, and subcortical ischaemic lesions.[12] Major cardiovascular risk factors are independent risk factors for the development of atherosclerosis and vascular dementia. These risk factors also predispose to acute stroke, which is a well established factor for the development of VaD. [13] The Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy (CADASIL), an early genetic small-vessel disease that causes lacunar strokes, ischaemic white matter lesions, and subcortical ischaemic vascular dementia has also been described.[12]

1.3.3 Lewy Body Diseases

Lewy bodies are eosinophilic cytoplasmic inclusions from damaged cytoskeletal component that contain deposits of a protein called alpha-synuclein. [14] Lewy bodies are present in both Parkinson disease dementia (PDD) and Lewy body dementia (DLB) with some differences in their distribution. In Parkinson disease it is found primarily in the subcortical regions of the brain, the midbrain, substantia nigra and locus ceruleus. In contrast, DLB is characterized by the presence of Lewy bodies in the subcortical and cortical (frontotemporal) regions of the brain. Amyloid plaques can also be found in DLB.[15] Both PDD and DLB belonged to the group called the “synucleinopathies”. [16]

a. Dementia with Lewy Bodies (DLB)

Dementia with Lewy bodies (DLB) account for 15-25% of dementia cases at autopsy. [17],[18] The cardinal features of dementia with Lewy bodies are: dementia, delirium (fluctuating cognition), early and vivid visual hallucinations and Parkinsonism. Any two of the supportive features of repeated falls, syncope, transient disturbances of consciousness, neuroleptic sensitivity, systematised delusions and/or hallucinations in other modalities, further strengthens the diagnosis. DLB is a distinct pathology, though there are overlaps between DLB and PDD, and DLB and AD.[19] In DLB, the onset of dementia and parkinsonism must occur within one year of each other, and either feature can be the initial symptom.[20] In PDD the motor features of parkinsonism predate the dementia by many years.

Dementia with Lewy bodies (DLB) differs from AD in that patients with DLB tend to have more problems with executive functions (planning, prioritizing, sequencing) and visuospatial impairment, but they tend to perform better with verbal memory. Both can co-exist, and diagnosis can be difficult as neither neuropsychological testing nor neuroimaging can reliably differentiates DLB from AD with accuracy.[21]

b. Parkinson Disease Dementia

The prevalence of dementia in patients with Parkinson disease is six times higher than in the general population. The prevalence of dementia in patients with PD was 24–31% and that 3–4% of the dementia in the general population is due to PDD. The estimated prevalence of PDD in the general population aged 65 years and older is 0.2–0.5%.[13] The development of PDD is associated with a two fold increased in mortality, caregiver stress, nursing home admission, and reduced quality of life.[22] There is usually a 10 to 15 year lag time between the Parkinson diagnosis and the onset of dementia.[13]

1.3.4 Frontotemporal Dementia

Frontotemporal dementia (FTD) is the most common cause of Frontotemporal Lobar Degeneration, a frequent cause of dementia in younger individuals with disease onset <65 years (mean age of onset is 52.8 to 56 years).[23],[24] It is characterized by behaviouralchanges and a dysexecutive syndrome. The other two syndromes in Frontotemporal Lobar Degeneration are: Semantic Dementia and Primary Non-fluent Aphasia, which feature language dysfunction and variable behaviouralabnormalities. Frontotemporal dementia (FTD) and Semantic Dementia each account for 40% of the Frontotemporal Lobar Degeneration, and Primary Non-fluent Aphasia accounts for the remaining 20%. [25] Frontotemporal Lobar Degeneration accounted for 20% of all cases of dementia [26]. About 38% to 40% of Frontotemporal Lobar Degeneration has a genetic component, of which 80% have an autsomal dominant pattern of inheritance.[27] Frontotemporal Lobar Degeneration is caused by the progressive dysfunction of the frontal and/or temporal lobes, with unilateral or bilateral involvement. Features that differentiate it from AD include social misconduct, hyperorality or akinesia and absence of perceptual disturbances. Memory is not predominantly affected.[28]

1.3.5 Mixed Dementia

There is increasing evidence that the brain lesions associated with AD and VaD often occur together. This coexistence of AD and VaD pathology is often termed mixed dementia. In an autopsy series from dementia clinics, it was reported that coexisting vascular pathology occurs in 24% to 28% of AD cases. Patients with mixed dementia are usually older and have more medical co-morbidities. The diagnosis and treatment of patients with both AD and VaD brain pathology is complex due to the lack of consensus on appropriate clinical criteria and terminology.[29] The term can also include other coexisting pathologies. Pathological Parkinson disease is present in 20% of patients with AD, and about 50% of patients with DLB have AD pathology. [30] ,[31]

1.4 DIFFERENTIAL DIAGNOSIS

Dementia has to be differentiated from delirium and depression. Either condition may co-exist with dementia (refer Table 1).

Table 1: Differentiating dementia, depression and delirium

SYMPTOMS	DEMENTIA	DEPRESSION	DELIRIUM
Onset	Insidious	Gradual	Acute
Duration	Months/years	Weeks/Months	Hours/days/weeks
Course	Gradually progressive	Worse in morning and improves at night	Fluctuates. Worse at night. Lucid period
Alertness	Normal	No interest. Responds usually as "don't know"	Fluctuates
Orientation	Usually impaired for time and place	Usually normal	Always impaired
Memory	Impaired recent and sometimes remote memory	Recent memory may be impaired. Remote memory intact	Impaired recent memory
Thoughts	Slowed, perseverance	Slowed, preoccupied, sad and hopeless	Often out of touch with reality
Perception	Often normal Visual hallucinations in 30-40%	20% with mood congruent hallucinations	Visual and auditory hallucinations are common
Emotion	Apathetic, labile, irritable	Flat, sad, unresponsive. May be irritable	Irritable, aggressive or fearful
Sleep	Disturbed, nocturnal wandering or confusion	Early morning awakening	Nocturnal confusion
Others		Past history or family history of mood	Other physical disease obvious

Adapted from 'Dementia touches everyone -a training guide for GPs'.[32]

A relationship between symptoms of Obstructive Sleep Apnea (OSA) and cognitive impairment has been identified in patients with dementia. [33] Patients with severe dementia were found to have significantly more severe obstructive sleep apnea, and those with more severe obstructive sleep apnea had significantly more severe dementia.[34]

2.0 PREVENTION, RISK FACTORS & EARLY IDENTIFICATION

It has been estimated that delaying the onset of dementia by five years would half its prevalence.[35] Hence prevention of dementia must be an ultimate goal. There has been much research into the prevention in dementia, but for any preventive strategies to be effective, several considerations need to be looked into:

Preventive strategies:

- ❒ Knowledge about risk factors
- ❒ Identifying the non-modifiable and the potentially modifiable risk factors, and
- ❒ Evidence that modifying the potentially modifiable risk factors could reduce the incidence of dementia

(NICE 2006) [13]

2.1 NON-MODIFIABLE RISK FACTORS

The confirmed risk factors for dementia are age and gender, which are not modifiable. Genetic/family history of dementia, intellectual disability and Down syndrome are also non–modifiable risk factors. [36]

2.1.1 Age

Advancing age remains one of the few confirmed risk factors for the development of dementia. The other confirmed risk factors are genetic, APOEε4 and Down syndrome. Prevalence of dementia doubles for every 4-5 years after the age of 65 years and those for VaD doubled every 5.3 years.[13] In a population study (n=1931), age ≥ 65 years was a risk factor for any dementia (Odds ratio (OR) =1.1) and for AD (OR=1.2). [37]

2.1.2 Gender

Prevalence studies show higher rates in women, especially for AD. The risk for all dementia and AD for the female sex was OR=1.7 and OR=2.0, respectively. [37]. Rates for VaD are higher in men, though the rates for women will equalise at older ages.[36]

2.1.3 Genetic

Early onset AD is generally defined as occurring before 60 years of age. It accounts for only 6%–7% of all cases of AD. Of this group, only 13% clearly exhibit autosomal dominant transmission. Early onset autosomal dominant forms of AD account for 1% of AD cases. [38]

Three causative gene mutations are identified; amyloid β-protein precursor (AβPP) on chromosome 21, presenilin 1(PS1) on chromosome 14 and presenilin 2(PS2) on chromosome 1. Among families in which causal genetic mutations for Early onsetAD have been identified, 30%–70% of mutations are in the presenilin-1 gene, 10%–15% are in the amyloid precursor protein gene, and less than 5% are in the presenilin-2 gene.[39]

No single causative genetic mutation has been identified for late onset AD. Most cases are a complex influence of genetic risk factors (e.g., the apolipoprotein E gene [APOE], sortilin-related receptor 1 gene [SORL1]) and environmental risk factors. APOE ε4 is the only robustly established risk factor for late onset AD. [40] Level III, fair

A systematic review of five population studies reported that APOE ε4 significantly increased the risk. The findings of APOE ε2 as reducing risk of dementia were not as robust. Only 2 studies were identified and the results were inconsistent. [41] Level II-3, fair

The strength of the association between the APOE ε4 allele and AD is stronger among women and people between 55 and 65 years old, but less so among older people. This may be because the risk of AD rises sharply in older age. Given all these uncertainties, genetic screening for the APOE genotype in asymptomatic individuals in the general population is not recommended due to low specificity and sensitivity. [39] Level III, good Patients suspected of having familial Early onsetAD should, however be referred to a memory or genetic clinic for further evaluation.[39] Level III, good

Recommendation
Genetic screening should only be done in a research setting. **(Grade C)**

2.1.4 Intellectual Disability and Down syndrome:

a. Intellectual disability (excluding Down syndrome)

The prevalence of dementia in people with learning disabilities without Down syndrome is raised to two to three times that expected in those aged over 65 years. Learning disability is an established non-modifiable risk factor for dementia. [13] , Level I, good)

In a recent epidemiological survey (n=228) of people with intellectual disability without Down syndrome aged 60 years and older, 28 patients (12.3%) met at least one set of dementia criteria.[42] Level III, fair

Dementia is common among people with intellectual disability.

b. Down syndrome

People with Down syndrome are at risk of developing dementia of Alzheimer type about 30-40 years earlier than the rest of the population. [13] Level I, good

In a cohort study of people with Down syndrome (n=506) aged 45 years and above, the prevalence of dementia over a period of four years was studied. It was found that up to the age of 49 years the prevalence was 8.9% (95% confidence interval (CI) 5% to 12%). The prevalence rate for the age group of 50-54 years was 17.7% (95%CI 12% to 23%), 55-59 years, 32.1% (95%CI 22% to 42%), and for 60 years and above the prevalence was 25.6% (95%CI 12% to 40%). [43] Level II-3, fair

Another cohort study followed up hospitalised adults with Down syndrome (n=92) for 15 years. Of the 87 participants who were dementia-free at the onset, 18 (21%) patients developed dementia during follow-up, with a median age of onset of 55.5 years. At the age of 60 years and above, a little more than 50% of patients still alive had clinical evidence of dementia. [44] Level II-2, fair

Down syndrome is an established risk factor for the development of dementia.

2.2 POTENTIALLY MODIFIABLE RISK FACTOR

The pathogenesis behind the aetiology of dementia involves several underlying mechanisms leading to neuronal loss and cell death. These mechanisms include the inflammatory hypothesis, role of antioxidants, 'use it or lose it' hypothesis and others. The potential effects of nutrition have become a topic of increasing scientific interest. There are arguments that nutrients such as vitamins, trace minerals, lipids can affect the risk of cognitive decline and dementia especially in frail elderly people at the risk of deficiencies.

These potentially modifiable risk factors will be grouped under three main headings:

- ❒ Cardiovascular risk factors: high blood pressure (hypertension), hypercholesterolemia, diabetes mellitus, folate and high homocysteine levels
- ❒ Lifestyle risk factors: obesity/being overweight, alcohol use, smoking, head injury, physical activity and education/mental stimulation
- ❒ Medication: NSAIDs, statins and antioxidants.

2.2.1 Cardiovascular Risk Factors

Major cardiovascular risk factors such as hypertension, smoking, hyperlipidaemia and diabetes are independent risk factors for the development of atherosclerosis and VaD. These risk factors also predispose to acute stroke, which itself is a well established risk factor for the development of vascular dementia. Indeed, cardiovascular risk factors are known to associate with dementia of all clinical types. [13] Level I, good

The Singapore guideline highlighted the fact that vascular risk factors should be considered and treated. [45] Level III, good

a. Hypertension

A systematic review and meta-analysis of four studies on hypertension demonstrated that there was a non-significant trend (relative risk (RR)=0.8, 95%CI 0.6 to 1.0) towards a reduction in dementia among treated subjects. This suggests that antihypertensive treatment may be a promising avenue for prevention of dementia, including AD and VaD. Furthermore there are already many evidence-based reasons for treating hypertension apart from reducing dementia risk. This includes reducing cardiovascular and cerebrovascular events. [13] Level I, good

Hypertension in the Very Elderly Trial Cognitive Function Assessment (HYVET-COG) showed there was no significant difference between treatment and placebo groups (hazard ratio (HR) 0.9, 95%CI 0.7 to 1.1). When these data were combined in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, the combined risk ratio favoured treatment (HR 0.9, 95%CI 0.8 to 1.0, p=0.045).[46] Level I, fair

In a recent systematic review of 16 longitudinal observation studies, a significant association between hypertension and risk of AD was reported, but this was achieved only by changing the criteria of hypertension, including altering the criteria levels for systolic (≥140 mmHg) and diastolic (both lower and higher) or changing the length of the observation (midlife). APOE 4 was the most consistent risk factor interacting with hypertension. The association with diabetes further increased risk. [41] Level II-2, good

Recommendation
Hypertension, occurring at mid-life (40-60 years) is a risk factor for dementia and should be appropriately treated. **(Grade A)**

b. Diabetes Mellitus

Diabetes is an established cardiovascular risk factor and is associated with mortality and significant morbidity. Emerging data suggests that diabetes mellitus is also a risk factor for dementia and cognitive decline in older persons.

A Swedish Health Technology Assessment report concluded that the evidence linking diabetes to dementia is moderately strong.[47] Level I, good A recent systematic review of 17 cohort studies found the relationship between diabetes and risk of AD to be complex. Most studies reported no significant association between diabetes and incident AD and few reported only a modest effect. It is only when diabetes is considered in association with other factors, particularly hypertension, that significant associations are reported. [41] Level II-2, good

A recent meta-analysis of 15 prospective cohort studies showed that the pooled adjusted risk ratio (RR) for all dementia when persons with diabetes were compared to those without, was 1.5 (95%CI 1.3 to 1.7). Summary RRs for AD and VaD comparing persons with diabetes to those without diabetes were 1.4 (95%CI 1.2 to 1.7) and 2.4 (95%CI 1.8 to 3.2), respectively. It was found that diabetes was associated with a 47% increased risk for all dementia, 39% for Alzheimers dementia, and more than two-fold risk for vascular dementia, among the community dwelling older adults. The association of diabetes to dementia was independent of cardiovascular co-morbidities. The results of the association between diabetes medications and risk of dementia were too heterogeneous to be conclusive. [48] Level II-2, good

Recommendation

Diabetes mellitus is a modifiable risk factor for the development of dementia and should be appropriately treated. **(Grade C)**

c. Hypercholesterolemia

Hypercholesterolaemia is a recognised risk factor for stroke, itself a major risk for VaD. Raised cholesterol level has also been implicated in AD.

A systematic review of 18 cohort studies (n=25,682), follow-up range 4.8-29 years (mean 13.3) looked at the association of total cholesterol and risk of AD, VaD and cognitive decline. It was noted that there was a consistent association between high midlife total cholesterol and risk of AD and any dementia. No study reported a significant association between midlife total cholesterol and VaD. The meta-analyses of late-life total cholesterol in relation to AD, VaD, and any dementia, did not reveal any significant association, suggesting the possibility that the effect of total cholesterol on dementia risk may be limited to midlife. There was only weak evidence for an association between total cholesterol and cognitive decline.[49] Level II-2, fair

There is insufficient evidence that hypercholesterolaemia increases the risk of dementia.

d. Homocysteine, vitamin B12, vitamin B6 and folic acid

Homocysteine, vitamin B12 and folate have been linked to cognition, dementia and mood. Deficiency in either vitamin leads to an increase in total serum homocysteine concentrations, and high homocysteine levels was found to disturb brain metabolism, as well as increased the risk of atherosclerosis and CVD. The prevalence of vitamin B12 deficiency in the elderly is 20%. Folate deficiency primarily caused by dietary deficiency is also common (10% prevalence) among the frail elderly population.[50]

The NICE guideline stated that raised homocysteine levels, associated with low folate intake and low folate levels, increased the risk of dementia, including AD. There is much interest in whether supplementation with B12 and/or folate may prevent the development of dementia and perhaps slow its progression. However supplementation has not shown any positive results. It remains a potentially modifiable risk factors [13] Level I, good

A Cochrane review on folic acid with or without vitamin B12 in the prevention of dementia (one RCT) and cognitive decline (three RCTs) provided no consistent evidence on the role of folic acid in dementia prevention. However the studies were too heterogenous to be conclusive.[51] Level I, fair

Vitamin B12 was not efficacious in reducing the risk of dementia and cognitive decline. This was based on a systematic review of three RCTs (three months duration) of healthy elderly and patients with dementia who were given vitamin B12 supplementation versus placebo.[51] Level I, fair

Another homocysteine related vitamin is vitamin B6 (pyridoxine). A Cochrane review of two RCTs of the effect of vitamin B6 on healthy elderly (n=297) against placebo over a period of 5-12 weeks, concluded that vitamin B6 had no overall effects on cognition or mood.[52] Level I, poor

Recommendation
Folic acid supplement, vitamin B6 or vitamin B12 should not be used for the prevention of cognitive decline or dementia. **(Grade B)**

2.2.2 Lifestyle risk factors

a. Smoking

Large prospective epidemiological studies have established that smoking is a risk factor for dementia in general and AD in particular. Smoking is clearly a risk factor for cardiovascular and cerebrovascular disease and as such increases the risk for stroke and vascular dementia.[13] Level I, good

In a more recent meta-analysis of prospective studies (n=19), it was found that elderly current smokers were at increased risk of dementia. Compared with never smokers, current smokers had 1.8 times (95%CI 1.4 to 2.2) risk of incident AD, 1.8 times (95%CI 1.3 to 2.5) risk of incident vascular dementia, and 1.3 times (95%CI 1.0 to 1.6) risk of any dementia. They also found that, compared with former smoking, current smoking was a significant risk factor for AD (RR 1.7, 95%CI 1.3 to 2.3) but not for VaD (RR 1.26, 95%CI 0.6 to 2.6) or any dementia (RR 1.3, 95%CI 1.0 to 1.8).[53] Level II-2, good

Another cohort study (n=6868) also found that current smoking at baseline was associated with an increased risk of dementia (HR 1.5, 95%CI 1.2 to 1.9) and AD (HR 1.6, 95%CI 1.2 to 2.0) when compared with never smokers. There was no increased risk for VaD (HR 1.4, 95%CI 0.7 to 2.8) found. There was also no association found between past smoking and risk of dementia (HR 1.2, 95%CI 1.0 to 1.4), AD (HR 1.2, 95%CI 0.9 to 1.4) or VaD (HR 1.2, 95%CI 0.7 to 2.2).[54] Level II-2, fair)

Smoking is a modifiable risk factor for dementia.

Recommendation
Smoking cessation is strongly advocated. **(Grade A)**

b. Alcohol consumption

Excessive alcohol consumption is an established risk factor for dementia. Epidemiological studies have shown that moderate alcohol consumption is associated with lower rates of dementia compared to either heavy drinking or abstinence. There is no consistent evidence to show that one type of alcoholic drink is more protective than another. [13] Level I, good

A more recent cohort study of over 16 years duration, found that any intake of alcohol predicted a 34% lower risk (HR 0.7, 95%CI 0.5 to 0.9) of developing dementia. Compared with those who are abstinent, the risk of developing dementia (HR) for those taking: 1-7 standard drinks per week were 0.7 (95%CI 0.5 to 0.9); 0.7 (95%CI 0.5 to 1.0) for 8-14 drinks per week ; and 0.4 (95%CI 0.2 to 0.8) for 15-28 drinks per week. [55] Level II-3, fair The general medical recommendation for safe drinking is up to 14 standard units per week for females and 21 standard units per week for males. [56], Level III, good

In a 34 year cohort study of women, (n=1462) consumption of wine was found to be protective for dementia (HR 0.6, 95%CI 0.4 to 0.8). [57] Level II-2, fair

A recent systematic review include a meta-analyses of 15 prospective studies (follow-ups ranged from 2 to 8 years).The participants comprised of AD (n=14,646), VaD (n=10,225) and any dementia (n=11,875). It was found that among older adults, light to moderate alcohol intake was associated with a 25%–28% reduction in risk of AD, VaD, and any dementia compared with alcohol abstinence. The pooled relative risks (RRs) of AD, VaD, and any dementia for light to moderate drinkers compared with nondrinkers were 0.7 (95%CI 0.6 to 0.9), 0.8 (95%CI 0.6 to 1.0), and 0.7 (95% CI 0.6 to 0.9), respectively.[333] Level 1,fair

Excessive alcohol consumption is a modifiable risk factor for dementia.

Recommendation

Excessive consumption of alcohol should be discouraged. **(Grade C)**

c. Obesity

Increased Body Mass Index (BMI) and increased body adiposity have been linked to increased risk of developing dementia. Several prospective studies have demonstrated an association between raised body mass index in mid life and an increased risk of dementia in general, and AD in particular. Obesity also increases the risk of developing type-II diabetes, which itself is a modifiable risk factor for the development of dementia. [13], Level I, good

A systematic review of four cohort studies (n=22,861) with a long follow-up of at least 20 years showed that elevated body mass index was associated with significant increased risk of dementia. [59] Level II-2, fair

A meta-analysis of seven prospective cohort studies of older adults demonstrated that the pooled OR for obesity and incident AD was 1.8 (95%CI 1.0 to 3.3), while that for obesity and VaD was 1.7 (95% CI 0.5 to 6.3). This study showed a moderate association between obesity and the risk for dementia and AD. [60] Level II-2, good

Recommendation
Obesity is a modifiable risk factor and maintenance of normal body mass index is recommended**. (Grade C)**

d. Head injury

Head injury is associated with loss of consciousness almost doubles the risk of dementia. However, a meta-analysis of 15 epidemiological studies demonstrated that this effect was specific to males only. [13] Level I, good

Mild to moderate traumatic brain injury was not associated with higher rates of amnestic mild cognitive impairment or dementia. The presence of APOE ε4 in traumatic brain injuries was not associated with cognitive changes.[61] Level II-2, good

For APOE ε4 allele-carriers, even fall-related head injuries which are not associated with explicit traumatic brain injury (TBI), was associated with an increased risk of dementia (HR 2.7, 95%CI 1.0 to 7.2).[62] , Level III, fair

Head injury associated with loss of consciousness is a risk factor for dementia

Recommendation
Road and occupational safety measures are recommended. **(Grade A)**

e. Exercise

There have been several population based studies on the association of exercise and dementia but no RCTs undertaken to investigate whether starting to engage in exercise for those who currently do not, will reduce their risk of developing dementia. It was concluded that there was insufficient evidence to recommend physical activity specifically as a preventive measure for dementia. [13] Level I, good ;[63] Level I, good)

A recent RCT (n=170) on volunteers who had subjective memory complaints but did not meet the criteria for dementia, were assigned to regular exercise for a duration of 24 weeks (150 minutes per week) versus usual care. It was found that the participants in the exercise group improved by 0.3 points (95%CI -0.9 to 0.5) and those in the usual care group deteriorated by 1.0 (95%CI 0.3 to 1.8) on the ADAS-Cog at 24 weeks. At the end of 18 months the participants in the intervention group improved by 0.7 points (95%CI -1.3 to 0.0) and the usual care group improved by 0.1 points (95%CI -0.5 to 0.9). [64] Level I, good

There is insufficient evidence that exercise reduced the risk of developing dementia.

f. Education and mental stimulation

Findings from two long-running studies of ageing and cognition, the Nun study and Religious order Study, have revealed that education helps protect people from the effects of AD. The more years of education, the greater the cognitive reserve. The likelihood that more poorly educated subjects will adopt unhealthy lifestyle behaviours has been suggested as an explanation for the stronger association found in subjects with types of dementia other than AD.

Lower educational attainment may be linked to subsequent development of dementia while cognitive training and participation in cognitively demanding leisure activities, may reduce risk of dementia. [13] Level I, good

A cohort study of non-demented subjects (n=931) on mentally stimulating activities at work, found that complex work, in particular complexity with data and people, was related to lower risk of dementia. The relative risk for those working with complex data (analysing, synthesising, coordinating, etc) was 0.6 (95%CI 0.4 to 0.8) and working with people (mentoring, negotiating, supervising, etc) was 0.6 (95%CI 0.4 to 1.0). In persons with lower education, highest levels of work complexity involving analysis and self-direction, could modify their dementia risk (RR 0.5, 95%CI 0.3 to 1.0). [65] Level II-2, good

However in another population-based study (10 years duration), the positive effect of work complexity were noted in those with vascular dementia only among subjects who had high complexity of work with people (HR 0.4, 95%CI 0.2 to 0.9) and high complexity of work with things (HR 0.5, 95%CI 0.3 to1.0).[66] Level II-2, good

Evidence from a systematic review showed that higher brain reserve was associated with a lowered risk for incident dementia by 46% (OR 0.5, 95%CI 0.5 to 0.6) wherein brain reserve is a composite of education, occupation, premorbid IQ and mental activities. Similarly, history of high occupational status was associated with decreased risk of 44% (OR 0.6, 95%CI 0.5 to 0.7, p<0.0001) compared to low occupational status. Protective effects of mentally stimulating leisure activities were independent of age, health, education and occupation (combined OR 0.5, 95%CI 0.4 to 0.6, p<0.0001). [67] Level I, good

In a recent systematic review of seven RCTs (n=3,194), it was found that cognitive exercise may confer a protective effect, showing a relative improvement of 1.2-2.6 points in the MMSE (95%CI 0.3 to 1.8). The study concluded that cognitive exercise training in healthy older individuals may produce protective effects on cognition. [68] Level I, poor

There is some evidence that low education level is a risk factor for dementia and AD.

Recommendation

Mentally stimulating activities should be continuously pursued throughout life. **(Grade C)**

g. Social network

Social isolation and unengaged lifestyle have been reported to be associated with accelerated cognitive decline in ageing. The term social network is used to capture the range of interactions, degree of engagement, marital status, support, contacts and activities. There are no RCTs that have looked at the protective effect of social networks on dementia. [69] Level III, fair

Compared to consistently high social engagement, low social engagement in both midlife and late life result in increased risk of dementia (HR 1.7, 95%CI 0.9 to 2.9), while men whose social engagement decreased from midlife to late life had a significantly higher risk of dementia (HR 1.9, 95%CI 1.1 to 3.1). [70] Level II-2, fair

There is insufficient evidence on the role of social engagement in reducing the risk of dementia.

2.2.3 Medication

a. Non-steroidal anti-inflammatory drugs

The role of non-steroidal anti-inflammatory drugs (NSAIDs) and the risk of dementia arise from the inflammatory hypothesis of AD. Fifty percent of retrospective studies found that NSAIDs is protective against dementia and cognitive impairment and 20% of prospective studies found an association with incident dementia but not with cognitive decline.

However it was concluded that further research is needed to establish dose, drug and duration of potential benefits with careful consideration of potential risks. [13] Level II-2, good

The Alzheimers Disease Anti-inflammatory Prevention Trial (ADAPT) research group performed a placebo controlled RCT comparing the use of naproxen (220 mg bd) or celecoxib (200 mg bd) against placebo in the development of incident dementia. The study was carried out on volunteers (≥ 70 years) with a family history of AD (n=2528). Events while on treatment versus placebo yielded HR of 2.0 (95%CI 0.8 to 5.0, p=0.14) for celecoxib and 2.4 (95%CI 1.0 to 5.8, p=0.06) for naproxen. The study did not support the hypothesis that celecoxib or naproxen prevents AD, at least within the early years after initiation of treatment. [71] Level I, fair

In another study, Szekely *et al* did an analysis of pooled data from six prospective cohort studies. They found that the risk of AD was reduced among those who reported use of any NSAIDs (HR 0.8, 95%CI 0.6 to 0.9; adjusted HR 0.8, 95%CI 0.7 to 0.9). [72] Level II-2, poor

A retrospective case control study that compared veterans over the age of 55 who developed dementia (n=49,349) against a matched control group (n=196,850), found that compared with no NSAID use, the adjusted OR for AD among NSAID users decreased from 1.0 for ≤1 year of use (95%CI 0.9 to 1.0) to 0.8 for >5 years of use (95%CI 0.7 to 0.9). Ibuprofen was the only NSAID that was found to reduce the risk of AD (OR decreased from 1.0 (95% CI 1.0 to 1.1) to 0.6 (95% CI 0.4 to 0.8)). Effects of other NSAID classes and individual NSAIDs were inconsistent. It was concluded that long-term NSAIDS (ibuprofen) use was protective against AD.[73] Level II-3, fair

Recommendation
Long-term usage of Non-Steroidal Anti-Inflammatory Drugs should not be used as a measure to prevent dementia as risks outweigh benefits. **(Grade B)**

b. Statins

Evidence from biological and epidemiological studies suggests that high levels of serum cholesterol may promote the pathological process that leads to AD. These findings raise the possibility that treating patients with cholesterol lowering agents might reduce the risk of developing AD.

Zhou *et al*, performed a meta-analysis on seven prospective and nested case-control studies (n=13,920) and showed that pooled RR of case-control studies was 0.3 (95%CI 0.2 to 0.5) while pooled RR for cohort studies was 1.2 (95%CI 0.9 to 1.5). When the two placebo controlled RCTs were pooled, the mean difference using ADAS-cog score was 1.8, which was not significant.[74] Level II-2, good

A prospective cohort study (n=1146) after adjusting for age, gender, education, and APOE 4 allele found that the use of statins was associated with less cognitive decline (p=0.0177). Similarly using logistic regression model on incidence of dementia showed that the use of statins may be associated with reduction in incident dementia (OR =0.3, p=0.067). [75] Level II-2, fair

Two prospective cohort studies analyzed the association of statins use and neuropathological changes in brain tissue after death. The first cohort (n=110) of cognitively normal subjects followed up for 12 years demonstrated that statins had significantly reduced risk for typical AD neuropathology.[76] Level II-2, good However, a recent study (n=929) did not find any association between statins and the risk of developing AD. (HR=0.9, 95%CI 0.5 to 1.5). [77] Level II-2, good

A recent Cochrane systematic review of two placebo controlled RCTs (n=26,340) found that statins given later in life to individuals at risk of vascular disease have no effect in preventing AD or dementia. [78] Level I, good

Recommendation
Statins are not recommended for the primary prevention of dementia or Alzheimers disease. **(Grade A)**

c. Antioxidants

One of the mechanisms causing neuronal degeneration is free radicals. Many studies have found evidence of increased level of oxidative damage to neurons and mitochondrial DNA in AD and MCI. Vitamin E functions biologically as a scavenger of different free radicals by working as an anti-oxidant.

There is a dearth of large scale prospective RCTs on the role of Vitamin C (ascorbic acid) and Vitamin E in the prevention of dementia. Vitamin E at higher doses increased all cause mortality, and as such Vitamin E should not be recommended for the primary or secondary prevention of AD or other dementias. [13] Level I, good

A cochrane review found only two RCTs on the use of Vitamin E, of which only one was on prevention (n=516), involving MCI patients on vitamin E (1000 IU bd). It showed no significant difference in the progression from MCI to AD (HR 1.0, 95%CI 0.7 to 1.4, p= 0.91). This systematic review concluded that there was no evidence of efficacy of Vitamin E in the prevention AD. [79], Level I, good

Recommendation
Antioxidants are not recommended for the primary prevention of dementia or Alzheimers disease. **(Grade A)**

3.0 EARLY IDENTIFICATION OF DEMENTIA

The development of dementia pathology occurred many years before the symptoms became obvious. Of interest is the transitional stage of cognitive impairment between normal aging and early AD, the state of mild cognitive impairment (MCI).

The concept of MCI evolved when early detection and identification of individuals at the pre-clinical stages of dementia became increasingly important in recent years. The diagnostic criteria for MCI subsume the presence of subjective memory complaints, preferably corroborated by a close informant, and documented by an abnormal performance on cognitive tests, adjusted for age and education.[80] These deficits must have no, or minimal, impact on global intellectual functioning and on the ability to perform ADL. The patient should not have evidence of dementia.[81] The MCI classification was recently expanded to encompass other cognitive domains, such as executive functioning and language, allowing the diagnosis of single and multiple-domain amnestic or non-amnestic MCI.

A meta-analysis showed that patients with MCI convert to dementia at rates of approximately 10% per year. [82] Level I,good A single-domain amnestic MCI may be a pre-dementia stage of AD whereas multiple-domain MCI may be a precursor to both AD and VaD. Single domain non-amnestic MCI may be found in the prodromal phases of FTD, VaD, DLB, or even depressive disorders.[83]

There were no studies that discussed the benefits of early identification of dementia. The NICE guideline states that, there is some evidence that early recognition and active therapy at the point of sharp decline in cognitive function delays the subsequent need for nursing home care and reduces the risk of misdiagnosis and inappropriate management.[13], Level I, good)

4.0 ASSESSMENT AND DIAGNOSIS

Assessment is an integral component of managing people with dementia. At the earliest opportunity, assessment may be done to screen people who are at risk of having dementia. Assessment tools are available for screening and diagnostic purposes as well as to determine the severity of dementia. Consequently assessment tools look at the level of cognitive and psychosocial impairment.

4.1 ASSESSMENT AT PRIMARY CARE

Primary care physicians are the gatekeepers to specialised services. The elderly are frequent users of primary care facilities. Despite this, majority of patients with dementia remain undetected and therefore do not receive the appropriate treatment. [84],[85]

4.1.1 Routine cognitive screening

More than 60% of patients made their first contact for treatment at the moderate or severe stage of illness, [86] ,[84] corresponding to 9-11 years after the onset of the first symptoms. [87] The growing number of at-risk elderly population and the availability of treatment options favour early screening in order to optimize the benefit of early treatment. However there is insufficient evidence to support routine screening of elderly people for dementia at primary care level. [13] Level I, good;[88] Level I, good

A cross-sectional study (n=3340) found that physicians identified only 18.7% of all patients with dementia. False positive rate for those screened positive was substantial and acceptance rate was poor as only 52% who screened positive agreed to go into the diagnostic assessment phase. The program was not effective in detecting dementia and due to high refusal rates, many cases would be missed as well. [89] Level III, good

In two longitudinal studies on subjective memory complaints (SMC) it was found that there was a higher association of SMC with incident dementia (OR= 2.2, 95%CI 1.2 to 4.0, p=0.008) in a cohort followed up for an average of 2.4 years. Despite this, it has a low predictive power of 14.1% (negative predictive value (NPV) of 81.6%). [90] Level II-2, fair There was a higher number of AD pathology amongst those with higher memory complaints (amyloid plaques, p=0.01 and tau tangles, p<0.001), which could not be explained by depression and other medical illness near to death.[91] Level II-2, good Another cross-sectional study found that among subjects with subjective memory complaints, depression need to be ruled out first. However delayed recall, if present, was a sensitive predictor of future cognitive decline.[92] Level III, fair

Questions to ask patients with subjective memory complaints
Modified from Jessen *et al*, 2007 [92] level III ,fair

1. Do you feel like your memory is becoming worse?
   Possible answers are: '**NO**' OR '**YES**'

2. Proceed to ask questions on the Subjective Memory Decline Scale[93]

(a) Do you have trouble remembering things that have happened to you recently?
(b) Are you worse at remembering where belongings are kept?
(c) Do you have trouble recalling conversations a few days later? AND
(d) Do you have more trouble remembering appointments and social gatherings?

The choices of answers are the following: (1) **NO** (2) **YES**
Any '**YES**' answer will require further assessment.

Source : Modified from Jessen *et al*, 2007, [91] level III ,fair

Recommendation

Routine screening in the primary care for dementia amongst the older population is not recommended. **(Grade A)**

Screening among those with subjective memory complaints is recommended. **(Grade B)**

Practitioners should have a high index of suspicion for dementia when patient has subjective memory complaints. **(Grade C)**

4.1.2 Screening instruments for people at risk of dementia

There are many types of tools found suitable for screening of patients at risk of dementia. The Mini Mental State Examination (MMSE) has been recommended due to its widespread acceptance and use. In addition, the Newcastle Mental Test Score, 7-minute Screen, General Practitioner Assessment of Cognition (GPCOG) and 6-items Cognitive Assessment Test has also been suggested. [13] Level I good

As most clinicians have limited time, there are other brief screening tools that are more practical to be used at primary care settings. A systematic review analysed and compared 22 instruments by their likelihood ratio (LR). Below is the list of brief instruments (Table 2) suggested according to the brevity of tests: [94] Level II-2 good

Table 2: Brief Screening Tests at Primary Care

No	Instruments	LR Positive	LR negative
1	7-Minute Screen	47	0.1
2	Memory Impairment Screen	33	0.2
3	Brief Alzheimer Screen	25	0.0
4	Mini-Cog	13	0.3
5	Abbreviated Mental Test	6 =12	0.4 =0.6
6	Short and Sweet Screening Instrument	11	0.1
7	Clock Drawing Test (CDT)	1.2 =7.7	0.1 =0.7
8	6-items Screener	7.3	0.2
9	Short Cognitive Evaluation Battery	6.3	0.1
10	Subjective Memory Complaints (SMC)	6.5 (informants) 1.8 (patient)	0.1 (informants) 0.4 (patient)
11	General Practitioner Assessment of Cognition (GPCOG)	4.8	0.2
12	3-Words Recall	4.3	0.4

A systematic review looked into patient-administered and informant-rated instruments. It was concluded that two instruments from the 16 reviewed, satisfied the criteria of good screening tools based on their psychometric and administration properties. The Concord Informant Dementia Scale (CIDS) and Informant Questionnaire on Cognitive Decline in Elderly (IQCODE) were brief and yet still retained reasonable accuracy.[95] Level II-2, good

An informant-rated instrument involves the administration of the various aspects of memory and intellectual function in everyday situation when compared to earlier in life.[96] A meta-analysis of 10 studies concluded that informant tests were as effective as brief cognitive tests at screening for dementia.[97] Informant-rated instruments such as the IQCODE, had also been found to be a better screening tool in large populations with varying degree of educational background. [98]

Combining an informant-rated instrument and cognitive testing increased the accuracy of prediction of dementia caseness compared to either tests used alone. [99] Level III, good;[100] Level III, good

In 2007, the Family Health Development Division of the Ministry of Health embarked on the cognitive screening programme at the primary care centers. A combination of informant-rated instruments such as Symptoms of Dementia Screener (SDS), and patient administered instrument, such as, the Elderly Cognitive Assessment Questionnaire (ECAQ), MMSE and 4-item Geriatric Depression Scale (GDS-4) were used.

The Symptoms of Dementia Screener (SDS) is a caregiver based tool. The results from a cross sectional study (n=103) using SDS showed that the Area under the curve (AUC)=0.9, with a standard error of 0.0 (95%CI 0.8 to 1.0). A cut off score ≥ 5, gave a sensitivity (Sn) 90.2%, specificity (Sp) 84.6%, positive predictive value (PPV) 85.9% and negative predictive value (NPV) 84.6%. This was compared against the MMSE cut off 23/24. For MMSE, Sn was 78.7%, Sp 92.2%, PPV 94.1% and NPV 75%. [101] Level III, good

The ECAQ is specifically designed to assess cognition among the elderly population in developing countries, taking into account the cultural difference and the relatively low literacy rate. This 10-items questionnaire had a Sn of 85.3%, Sp of 91.5% and PPV of 82.8%. Both the inter-rater and the test-retest reliability were good at 0.8 and 0.9 respectively.[102]

The short version of geriatric depression scale (GDS) had been found to be as effective as the long scales in screening for depression in the older people. A cross sectional study comparing the four items against the 15 items and 30 items, found that GDS-4 did not differ from the longer scales in terms of accuracy. [103] Level III (Refer to Table 3)

Table 3: Accuracy of different versions of GDS

Test	Sn	Sp	PLR	NLR	AUC-ROC
GDS-4	82%	67%	2.5	0.3	0.8 (0.7 to 0.9)
GDS-15	82%	60%	2.1	0.3	0.8 (0.7 to 0.9)
GDS-30	100%	62%	2.7	0.0	0.9 (0.8 to 0.9)

Recommendation

A caregiver based questionnaire (e.g. Symptoms of Dementia Screener) is to be used before proceeding with a more detailed screening. **(Grade C)**

Appropriate tools that can be used for detailed screening include MMSE or ECAQ and GDS-4 to be used. **(Grade C)**

4.1.3 Referral of patients with dementia to specialist services (secondary/tertiary)

Patients with dementia may require referral to specialist services (memory clinics where available) after initial management at primary care level. Two guidelines recommended that while most cases of dementia can be diagnosed and managed by primary care clinicians, some cases may require referral to specialist services for diagnosis, management and special care [104], Level III, fair;[105] Level III, fair (Refer to Table 4)

Table 4: Summary of reasons for referral to specialist care services are:

1	Issue of diagnosis, including for second opinion	a , b
2	Difficult behaviour problems	
3	Psychiatric co-morbidity e.g. depression	
4	Treatment issues, including accessibility to certain drugs	
5	To obtain community support services	
6	Age is less than 60 years old	a
7	Rapid deterioration in clinical condition	
8	Possible industrial exposure to heavy metal	
9	Genetic counselling	b
10	To involve other health care professionals in management	

a = Australia Practice Guidelines 2003 b = Royal College of Psychiatrist 2005

In the local context, due to the lack of expertise and human resource at the primary care level, all patients suspected of dementia, should be referred to the secondary/tertiary services or memory clinics.

Recommendation

All patients with suspected dementia should be referred to a geriatric psychiatrist, psychiatrist, geriatrician or wherever available a memory clinic, for a more comprehensive assessment. **(Grade C)**

4.2 MEMORY CLINIC

According to a United Kingdom National Audit Office report (2007), two-thirds of patients with dementia in England receive no formal diagnosis or have no contact with specialist services at any time during their illness. Furthermore, some hospital services avoid dementia diagnoses because of concerns about their capability and resources, and fears that the diagnosis might delay a patient's discharge.[106]

In its five-year National Dementia Strategy (NDS), the Dept of Health UK endorsed the creation of a network of memory clinics throughout their country, staffed by a multidisciplinary team. This enables referrals from GPs to clinical specialists based in memory clinics. The aim is to improve dementia care and early diagnosis.[107] Level III, good)

Memory clinics have become acceptable and useful vehicles for improving the identification, investigation, and treatment of memory disorders, including dementia. They are provided in various settings; the setting determining clientele and practice. All aim to facilitate referral from GPs, other specialists, or by self referral, in the early stages of impairment, and to avoid the stigma associated with psychiatric services.[108] Level III, good NICE Guideline recommends memory clinics for service provision with a multi-disciplinary approach from old age psychiatrists, nurses, allied health staff and social workers. [13] Level I, good

In keeping with this, the European Dementia Consensus Network also recommends provision of memory clinics with an emphasis on multidisciplinary collaborative care for both early, accurate diagnosis and management. Here, close collaboration between GPs and specialised memory clinics may be the ideal model. [109] Level III, fair

Besides hospital-based or centralised memory clinics, an alternative model for memory clinic is a primary care-based practice with specialist input, for greater outreach and greater acceptability. [110] Level III

A cohort study (n=290) of consecutive referrals demonstrated that specific services for early dementia increased the identification of people with early dementia and provision of adequate care. Those receiving such services appear to improve in terms of quality of life and BPSD. Furthermore such memory services can be incorporated within the local services. Acceptability is also greater when it is seen as a memory services rather than services defined under old age psychiatry or mental health. [111] Level II-2, good

Multidisciplinary team consists of:

Core team members

- Clinicians - Geriatric psychiatrist/geriatrician/neurologist
- Medical Officers
- Psychologist
- Nurses/Psychiatric nurses
- Occupational therapist
- Physiotherapist

Supportive members

- Primary care physician
- Home care nurses/community nurses
- Dietician/Nutritionist
- Social worker
- Speech therapist
- Pharmacist
- Alzheimers Society representative

Recommendation

Memory clinic with a multidisciplinary team should be set up at secondary and tertiary care level. **(Grade C)**

4.3 ASSESSMENT OF DEMENTIA AT THE SECONDARY/TERTIARY CARE LEVEL

A more comprehensive clinical evaluation of all the three domains of cognition, behaviour and function will be required in those suspected of dementia, with the aims of making an early diagnosis, assessing complications and determining the causes of dementia.

It is important to exclude delirium (acute confusional state), especially when the presentation is acute in onset. If the onset of symptoms is subacute (weeks to months), then the exclusion of obstructive sleep apnea (OSA), depression and other neurological conditions, need to be made as most of these conditions are treatable.

4.3.1 History Taking

The basis of any clinical evaluation is in getting a detailed history, which should encompass the mode of onset of symptoms, course of progression, pattern of cognitive impairment and the presence and pattern of the non-cognitive symptoms. History from a reliable informant is mandatory. [63] Level I, good

Practical questions to assist in the diagnosis using the DSM-IV criteria (refer to Appendix 5).

4.3.2 Physical examination

Physical examination, particularly neurological examination is essential in the differential diagnosis of dementia.

4.3.3 Brief cognitive tests

Mental state examination would encompass assessment of cognitive function which can be made by using brief cognitive instruments, or a more detailed neuropsychological assessments administered by a clinician or neuropsychologist. There are many brief cognitive tests that can be used to obtain an objective measure of the cognitive impairment.

Neither the NICE-SCIE guideline, SIGN and Swedish Health Technology Assessment make any specific recommendations as to which cognitive tests to be used. The tests listed below are simple and easy to use at the clinic setting, with fair to good evidence. The Singapore Guidelines recommend some instruments that had been validated for its population (e.g. ECAQ, Abbreviated Mental Test, Chinese MMSE and Vascular Dementia Battery Test).

> It is well to remember that a diagnosis of dementia can only approach a high level of accuracy if the clinician follows up the patient for many years and/or compares multiple assessment instruments. [112]

a. Mini Mental State Examination (MMSE) (Folstein)

The most commonly used cognitive test is the MMSE. The MMSE score and cut-off values are affected by several factors including educational levels, age, and ethnic differences. Certain component of the MMSE may be more reliable in pointing towards the diagnosis, rather than the total score.

The cut-off value for MMSE had to be adjusted according to the education levels of the subject. A cut-off scores of 27 gave Sn 0.9, Sp 0.9, PPV 0.8, NPV 0.9 and a cut-off of 28 (Sn 0.78, Sp 0.8, PPV 0.6, NPV 0.9) in the higher educated subjects yielded a better diagnostic accuracy, in both the cognitively intact and cognitively impaired subjects among the Caucasians and English speaking subjects. [113] Level III, fair

The AUC values for the MMSE ranged from 0.9 to 1.0, indicating excellent overall accuracy at identifying dementia across age and education stratifications. The lowest AUC value (0.8) occurred in the group aged 97 and older with the least education. The highest AUC value (1.0) was for group aged 90 to 93 with vocational school or some college education. However when using MMSE in the 90 and older age groups, age and education related adjustments should be considered. [114] Level III, good

The differences in MMSE were most pronounced among the non-educated and lower educated subjects, with the MMSE showing a lower Sp (62.8%) and a lower LR (2.6) among the Malays. A cut-off value of 23/24 among the better educated yielded AUC-ROC at 94.8%, Sn of 97.5%, Sp of 75.6%, and a LR of 4.0. [115] Level III, good

A recent cross sectional study to validate the Malay version of MMSE (M-MMSE) was done on 300 subjects (24.3% with dementia vs 75.5% controls) using 3 versions: M-MMSE-7(serial 7), M-MMSE-3 (serial 3) and M-MMSE-S (spell 'dunia' backwards). It was found that the optimal cut-off scores varied with each version and education level. Gender adjusted cut-off scores should be applied in those with lower education. The validity of the M-MMSE for the 3 versions are listed below (Table 5).[116] Level III, good

Table 5: Cut off values & accuracy of the different versions of the Malay MMSE

	M-MMSE-7 (n=300)	M-MMSE-3 (n=160)	M-MMSE-S (n=145)
Optimal cut-off	21/22	18/19	17/18
Sensitivity	88.5	97.1	97.7
Specificity	75.3	90.0	93.3
PPV	53.7	57.6	62.5
NPV	95.5	99.2	100.0
AUC	0.9	1.0	1.0

Details of the Malay Mini Mental are available in Appendix 3.

MMSE has been compared with other cognitive screening instruments such as Clock Drawing Tests (95%CI 0.64, 0.6 to 0.7) [117] Level III, fair, Verbal Fluency (65-66%) and Blessed Dementia scale (67-72%), and were found to be well correlated. [118] Level II-2, fair

b. Verbal Fluency (VF)

There are two types of verbal fluencies-categorical (semantic) verbal fluency (e.g: categories of fruits, vegetables, animals) and phonemic (letter) verbal fluency, involving letters starting with F, A, and/or S.

A meta-analysis showed that patients with AD showed more impairment in categorical (semantic) fluency irrespective of the MMSE scores ($r=0.7$, $p<0.001$). [119] Level I, good

It had also been shown that verbal fluency was sensitive to early memory changes, but had to be used with other non-fluency measures.[120] Level III, fair The test was associated with specific psychological functions at different stages of cognitive impairment as suggested by the different cognitive predictors of Categorical Verbal Fluency Test (CVFT) scores in the healthy and the questionable dementia or mild cognitive impairment group. [121] Level III, good

Verbal fluency could be influenced by education, and so the cut-off scores had to be adjusted according to the educational levels (0 years: 9 (Sn 90.5% and Sp 80.6%); 1-3 years: 12 (Sn 95.2% and Sp 80.0%); 4-7 years: 12 (Sn 91.3% and Sp 91.9%) and ≥ 8 years: 13 (Sn 82.6% and Sp 100.0%). [122], Level III, good It was not influenced by repeated learning in patients (n=69) with MCI or dementia. [123] Level III, poor

Categorical (Semantic) fluency test may assist in the early detection of dementia. The LR indicated that a score of <15 is 20 times more likely to occur in an individual with AD as opposed to a person without AD.[124] Level III, fair

c. Category naming

A meta-analysis of 21 studies (n=1066) on subjects with AD and controls showed that patients with AD, were better at naming living things if it is presented in colour (significant difference between monochrome (1.5, 95%CI 1.9 to1.3) and colour (2.6, 95%CI 4.1 to 1.7). However the studies showed some heterogeneity (Q_{wi}=36.1, p=0.007). There were also gender differences seen, with female patients having more problems in naming living things compared to non-living things (for living things only the proportion of males approached significance (p=0.06) and for non-living things, the proportion of males were significant (p=0.03)) [125] Level I, fair

d. Clock Drawing Test

The clock drawing test was found to be a reliable screening instrument for dementia but was influenced by age, gender and education. [126] Level III, good In the older person with less than four years of education, it was certainly not a valid screening test for dementia. [127] Level III, good

The Clock Drawing Test can be done by drawing to command (CLOX I) or drawing to copy (CLOX II). Both showed a high AUC-Receiver Operating Characteristic (ROC) at 84% and 85% respectively.[126] Level III, good

There are many types of scoring systems available of which, the best was the three-factor system, using quantitative and qualitative scoring (e.g. Sunderland scoring). It showed a high inter-rater correlation and classification agreement of 0.9-1.0 for AD, but a weak correlation with mild dementia (kappas of 0.2 to 0.4). [128] Level III, good) Another study however, did not find any differences among the different scoring systems. [127] Level III, good

Clock Drawing Test that required time setting showed a high Sn (81% to 93%) and low Sp (49% to 60%). Misdiagnosis was low as shown by the Overall Misclassification Rate (OMR) of 0.2 to 0.3. [129] Levels III, good Clock Drawing Test also had a fairly good accuracy in discriminating between FTD from AD and normal subjects, correctly identifying 88.9% of FTD and 76% of AD patients with an overall prediction accuracy of 83.6%.[130] Level III, good A good alternative was the Clock Reading Test as both Clock Reading Test and Clock Drawing Test showed significantly good correlation of r=0.5. [131] Level III, fair

e. Montreal Cognitive Assessment (Nasreddin)

The Montreal Cognitive Assessment (MoCA) is a simple and brief screening instrument better at identifying MCI (Sn 90%, Sp 87%) and early AD (Sn 100%; Sp 87%) compared to the MMSE [MCI (Sn 18%) and AD (Sn 78%)] [132] Level II-2, good. MoCA was also sensitive in detecting mild cognitive impairment in patients with Parkinson Disease. [133] Level III, fair

The usual cut-off scale for MCI was 26/27, among the Western population with at least 12 years of education. It had to be validated to the culture and educational background of the subjects, as seen in the Korean version which predicted a better accuracy at a lower cut-off (22/23; the Sn of 89% and 98% to MCI and AD respectively, with a good Sp of 84%). [134] Level III; good

This instrument can be downloaded from *www.mocatest.com.*

f. Clinical Dementia Rating Scale (Morris)

The Clinical Dementia Rating (CDR) can be used for the detection of MCI and mild dementia as shown by the poor performance on the other cognitive neuropsychological assessments. Use of CDR was influenced by subject's educational level, 57% concordance rate in those with less than two years of education. [135] Level III, fair The CDR-Sum of Boxes (CDR-SOB) may be a better indicator of questionable dementia rather than the CDR global scores. [136] Levels III, poor

4.3.4. Neuropsychological test

Cases presenting with subtle cognitive deficits will require a more comprehensive assessment, using specific neuropsychological test batteries, beyond the capabilities of the clinician. A series of tests administered by a clinical psychologist will require at least two to three hours of testing, covering the aspect of intelligence and memory, assessment of psychomotor speed, information processing, attention and concentration, and the higher executive function.

Neuropsychological tests are also useful in determining the subtypes of dementia such as AD, FTD, DLB and VaD. It can also help in differentiating these dementia subtypes from depression, when the features are not very clear cut.

Recommendation
History, physical and neurological examination remains an important component of assessment of dementia. **(Grade C)**
At the secondary/tertiary level, the brief cognitive tests that can be used include the MMSE, categorical verbal fluency (CVFT), category naming, Clock Drawing Test (CLOX-I or CLOX-II) or Clock Reading Test and Montreal Cognitive Assessment. **(Grade C)**
When the diagnosis of dementia is inconclusive, then neuropsychological tests will be required. **(Grade C)**
All tests need to be validated for the culture, language and educational level of the population. **(Grade C)**

4.3.5 Assessment of Behaviour and Psychological Symptoms of Dementia

Behavioural changes are present in most individuals with dementia, becoming increasingly common as dementia progresses.[137] Behaviour and Psychological Symptoms of Dementia (BPSD) or neuropsychiatric symptoms, such as depression, anxiety, agitation, paranoia, hallucinations and sleep problems, are seen in up to 90% of AD patients in the Asian countries, similar to that in the Western countries. [138];[139];[140] Aggression and agitation which occur in 30% to 50% of patients with dementia,[141] is of great concern because it is a major antecedent to institutionalisation,[142] increases costs and caregiver burden, and leads to an overall poor prognosis.[143];[144] Hence BPSD should clearly be documented and assessed in PWD.

These behavioural problems can be rated objectively using behaviour scales which may be either self-rated, caregiver-based or observer reports. Some of the scales that can be used include the Neuropsychiatric Inventory (NPI) [145], Brief Psychiatric Rating Scales (BPRS) [146] or Behavioural Pathology in AD Rating Scale (BEHAVE-AD).[147]

Both the NICE and the SIGN guideline suggested that all PWD should be assessed for depression, in view of its high prevalence. These guidelines did not make any recommendations on the instruments to be used for the assessment of depression in dementia. [13] Level I, good;[63] Level I, good) However, the Singapore guideline suggested that the Geriatric Depression Scale (GDS)[148] and the Cornell Scale for Depression in Dementia (CSDD) [149] could be used but did not mention the diagnostic accuracy of these instruments. [45], Level III, good

It was found that both the Montgomery-Asberg Depression Rating Scale (MADRS) [150] with a ROC-AUC of 0.9 and the CSDD (ROC-AUC of 0.7), performed well in distinguishing depressed from the non-depressed patients with early onset dementia ($p<0.044$). However MADRS had a strong correlation with CSDD ($rs=0.8$, $p<0.001$), and the NPI subscales of dysphoria ($rs=0.7$, $p<0.001$) and apathy ($rs=0.6$, $p<0.001$). [151] Level III, fair

People with dementia may not exhibit the typical features of depression as outlined in DSM-IV criteria. The National Institute of Mental Health Depression in Dementia criteria (NIMH-dAD) (Sn 94%, Sp of 85%, PPV 77% and NPV 96%) was able to identify patients with dementia who were depressed better than the criteria for DSM-IV Major Depression (14%, $p<0.001$) or the DSM-IV criteria for Major or Minor depression (36%, $p=0.021$) and as well as CSDD (30%, $p=0.004$) and the GDS (33%, $p=0.0041$) at the established cut-off points. [152] Level II-3, good

Recommendation
Behaviour problems in people with dementia should be enquired on a routine basis and rated qualitatively where possible. Suggested scales include NPI, BPRS and BEHAVE-AD. **(Grade C)**
All patients with dementia need to be assessed for depression. **(Grade A)**
The National Institute of Mental Health Depression in Dementia criteria (NIMH-dAD) can be used to make a diagnosis of depression in people with dementia. **(Grade B)**
The diagnosis and severity of depression in dementia can also be determined using qualitative scales such as the Geriatric Depression Scale OR Cornell Scale for Depression in Dementia. **(Grade C)**

4.3.6 Assessment of Functional Impairment

Functional impairment can be assessed based on the activities of daily living (ADL). Basic activities of daily living (BADL), relates to the day-to-day core survival abilities, while instrumental ADL (IADL), defined by their higher level of complexity, reflects the ability to live independently in the community. Difficulties in performing ADL are progressive in AD and the related dementias, involving IADL to a greater extent than BADL. [153] There are many scales available to assess ADL which can be rated subjectively by the patient or objectively by the caregiver or observer.

The different dementia subtypes may differ in terms of their ADL. Patients with AD may have less impairment in their ADL compared to those with FTD or DLB. Those in the latter groups did not only differ in distinctive profiles of functional impairment, but also in the specific types of activities.[154];[155] Persons with MCI showed slower speed of task performance and clinically significant functional impairments, particularly on informant-based measure. [156]

In a systematic review of five studies using four types of ADL scales: Index of ADL [157]; IADL Scale [158] Modified Blessed Dementia Scale [159] and Functional Activities Questionnaire [160] the sensitivities and specificities obtained when used for population screening were shown below (see Table 6). However there may be some bias in the result, in view of the heterogeneity of the studies in terms of age of the subjects and different literacy levels. There was also no adjustment done for gender. [161] Level I, fair

Table 6: Sensitivity and specificity - Activities of Daily Living (ADL) scales

	Principal author	Functional scale	N	Sn (95% CI)	Sp (95% CI)
1	Juva	DS (Blessed)	391	84.0 (80.0–87.3)	82.0 (77.9–85.5)
2	Juva	IADL	426	91.0 (87.9–93.4)	86.0 (82.4–89.0)
3	Juva	FAQ	370	94.0 (91.1–96.0)	84.0 (79.2–87.4)
4	Barberger-Gateau	IADL	2763	94.0 (93.1–94.8)	71.0 (69.3–72.7)
5	Bermejo	FAQ	3936	90.8 (89.9–91.7)	90.6 (89.7–91.5)
6	Beland	IADL	430	92.1 (89.2–94.3)	91.5 (88.5–93.8)
7	Beland	FAQ	430	98.4 (96.7–99.2))	89.0 (85.7–91.6)
8	Garcı´a	IADL	3214	85.0 (83.7–86.2)	66.0 (64.3–67.6)
Total	8		11,960		

Recommendation

All people with dementia will need to be assessed on their activities, both in basic activities of daily living and instrumental activities on a routine basis. **(Grade C)**

4.4 DIAGNOSTIC CLASSIFICATION

Ascertain that the patient meets the clinical criteria of dementia, as defined by either the International Classification of Diseases-10 (ICD-10) or the Diagnostic Statistical Manual (DSM-IV (1994) or DSM-IV-TR (2000)). Most of the available criteria are based on the presence of clinically significant cognitive change over time. [162]

History remained essential in diagnosing dementia. Among the criteria of dementia, DSM-IV have the highest agreement with history (k=0.8) compared to DSM-III-R and history, (k=0.8).[163] Level II-2, fair

The final step in the clinical evaluation is to determine the dementia aetiology or subtype, as this will determine the management and treatment, including the decision on starting specific drug therapies. According to the two systematic reviews. [13] Level I, good ;[164] Level I, good the DSM-IV-TR and ICD-10 definitions of dementia are often appropriate in AD where memory is always affected but not always appropriate for VaD, FTD or DLB where memory is not predominantly impaired. The NICE guidelines listed the diagnostic criteria for each specific dementia subtypes.

The AD criteria mentioned in the Singapore Guidelines include the DSM-IV criteria [165] and the National Institute of Neurologic, Communicative Disorders and Stroke–AD and Related Disorders Association Work Group (NINCDS-ADRDA) criteria for AD [166] The National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-AIREN),[167] Alzheimer Disease Diagnostic and Treatment Centre (ADDTC) criteria for VaD[168] and the Hachinski Ischemic Score (HIS) [169] and Modified HIS [170] can be used for VaD. Table 7 summarises the different criteria for the dementia subtypes. Details of ICD-10 and DSM-IV-TR are available in Appendix 4 and 5 respectively.

4.4.1 Diagnostic criteria for dementia subtypes

a. Alzheimer Disease

The clinical diagnosis for AD can be made using the clinical DSM criteria or the NINCDS criteria. The latter criteria were mainly used in research. For probable AD, both DSM-III-R and NINCDS-ADRDA have reasonable Sn (81%) and Sp (70%). For possible AD, the NINCDS-ADRDA criteria had a higher sensitivity but a much lower specificity (48%). [13] Level I, good

The specificity and sensitivity of the clinical diagnosis of AD against the neuropathological diagnosis was 75.9% and 60.6% respectively. Neuropathological investigations remained critical to determining dementia diagnosis.[171], Level II-2, poor

In an analysis of three epidemologic studies (n=175) comparing the clinical and neuropathologic diagnoses, it was found that the sensitivity of a clinical diagnosis of probable or possible AD was 93%, with an overall diagnostic agreement of 81%.[112] Level II-2, good.

b. Vascular Dementia

For VaD, DSM-IV and NINCDS-AIREN showed poor validity and inter-rater reliability. The sensitivity with all criteria tend to be low (50%), but the specificity was good (85%). [13] Level I, good The Alzheimer Disease Diagnostic and Treatment Centre (ADDTC) criteria for VaD and the criteria for Vascular Cognitive Impairment (VCI) showed better sensitivity (88%) and specificity (75%), against post mortem confirmed diagnosis, if used by an experienced rater. [172], Level II-2, fair

c. Lewy Body Disease (DLB and PDD)

The consensus criteria for DLB had low sensitivity but high specificity. [13] Level I, good In a recent study, it was found that there was a good correlation between clinically probable DLB using the 3rd Consortium Dementia of Lewy Bodies criteria and the pathological criteria (>95%), on 52 patients with DLB. [173] Level II-2, fair

Dementia with Lewy Body (DLB) and PDD are separated by the duration of Parkinsonian features which has to be present for more than a year before the onset of dementia for PDD, and less than a year for DLB.[13] Level I, good

d. Frontotemporal Dementia

For the diagnosis of FTD, the current consensus criteria lacked sensitivity (36.5%) for FTD if based on neuropsychological profile alone (specificity was 100%, PPV 100% and NPV 64%), but when used with MRI, the sensitivity (63.5%) improved (Sp 70.4%, PPV 65.6%, NPV 68.5%). The used of SPECT/PET improved sensitivity further to 90.5% (Sp 74.8%, PPV 76% and NPV 89.8%). [174] Level III, fair

The presence of the 5 core diagnostic criteria (Lund-Manchester criteria) for FTD had a sensitivity (79%), specificity (90%) with moderate positive LR (8.1) but good negative LR (0.2). [175] Level II-2, fair

e. Mixed Dementia

None of the diagnostic criteria currently available deals with mixed causes of dementia. Until further evidence emerges, it is pragmatic to consider the condition that it fits best. [13] Level I, good

f. Mild Cognitive Impairment

There was no mention of any criteria for MCI in both the systematic reviews. [13];[63] The definition of MCI varies according to the tests used for case definition. [176] Level III; fair) The predictive accuracy of MCI, using the Petersen's criteria, against AD was good only for amnestic MCI in older subjects (AUC for > 80 years = 0.8 versus AUC for aged 55-69 = 0.7). [177] Level III, good

Table 7: Diagnostic criteria for subtypes of dementia

Alzheimer Disease [13]	**Vascular Dementia**[13]	**Lewy Body Disease (DLB and PDD)**	**Frontotemporal Dementia**[13]
ICD-10 (Refer Appendix 4)	ICD-10 [178]	The third consensus criteria for Dementia with Lewy bodies [20]	Lund Manchester Criteria [179]
DSM-IV-TR [165] (Refer Appendix 6)	DSM-IV-TR[180]		The NINDS Workgroup on Frontotemporal Dementia and Pick's Disease[181]
NINCDS-ADRDA [141]	NINDS-AIREN[167]		
	Modified Hachinski Ischaemic Score (MHIS) [169],[170]		
	The California Alzheimers Disease Diagnostic and Treatment Centers (ADDTC) (criteria for Ischaemic VaD[168]		

Recommendation
The diagnosis of the subtypes of dementia should be determined using the specified diagnostic criteria. **(Grade B)**
The DSM-IV, ICD-10 and the NINCDS-ADRDA criteria should be used to diagnose Alzheimers disease. **(Grade A)**
The diagnosis for Vascular dementia and Vascular Cognitive Impairment (VCI) remains difficult. The Hachinski Ischemic Score may be useful in the diagnosis in the clinical setting. **(Grade B)**
The DSM-IV and the NINCDS-AIREN criteria may be used in the diagnosis of vascular dementia in research setting. **(Grade B)**
The Lund-Manchester Criteria should be considered when frontotemporal dementia is suspected. **(Grade B)**
The Third Consortium Dementia for Lewy Bodies criteria should be considered when making a diagnosis for DLB. **(Grade B)**
The Petersen's criteria may be considered when making the diagnosis of amnesic (Mild Cognitive Impairment) in older patients. **(Grade C)**

The diagnostic definition is still unclear for Mixed dementia and other types of Mild Cognitive Impairment.

4.5 Progression and severity of dementia

As dementia is a progressive disease, staging tools can be used as surrogate markers of severity. The multiple domains involved in dementia mean that, there are a variety of tools available that can assess the global severity, cognitive and functional impairment of the PWD. These tools would require information from an informant. It may also be useful in monitoring the response of the patients to the drug therapy.

Instruments that were often used include the MMSE, Global Deterioration Scale (GDS)[182], CDR, Functional Assessment Staging (FAST)[183] and others.

The CDR discriminates well with the MMSE (see Table 8) in all stages of dementia severity as shown by the Cohen's kappa ranging from moderate to severe: (0.4) for MMSE 30 /CDR 0 (no dementia); (0.5) for MMSE 25-21/CDR 1 (moderate dementia); (0.7) for MMSE 20-11/CDR 2 (moderately severe); (0.7) for MMSE 10-0/CDR 3 (severe)); except in cases of questionable dementia, where the kappa was fair (0.2 to 0.3). [184] Level III, fair

Table 8: Severity of cognitive impairment based on MMSE

Mild	MMSE 21 to 26
Moderate	MMSE 15 to 20
Moderately severe	MMSE 10 to 14
Severe	MMSE 0 to 9

The CDR has good convergent validity against clinical features (87% agreement, k=0.8 for all dementias), psychometric tests, and even better than DSM-III-R (agreement 85%, k = 0.8 for all dementias at all stages) and at discriminating milder stages of dementia (agreement 82%, k=0.8). It is less susceptible to educational, linguistic and social-cultural influences (r= 0.1, p=0,204) or age (r= 0.0, p=0.47). [185] Level II-2, fair CDR and the DSM-III-R diagnosis showed a good agreement for most stages of severity (k=0.8), except for questionable or mild dementia (DSM-III-R, k=0.2), where CDR was better, especially in a multi-ethnic, low educated population. [186] Level III, fair

CDR is also shown to be highly correlated to the global deterioration scale (GDS), in rating the severity of dementia (r 0.9), in both AD and VaD group. [187] Level II-2, good

In questionable dementia or MCI, a combination of clinical assessment on function, and episodic memory tests, particularly verbal and visual measures can predict the progression to AD.[188] Level II-2, fair

Recommendation
The Clinical Dementia Rating Scale and Global Deterioration Scale may be used as both are equally sensitive in mild cognitive impairment and early dementia. **(Grade C)**
When a definite diagnosis of dementia has been established, any of the scales suggested (MMSE, Global Deterioration Scale, CDR, Functional Assessment Staging) for determining progression may be used. **(Grade C)**

4.6 Screening for co-morbid medical conditions

Screening for co-existing medical problems, should be a regular practice for all clinicians, as co-morbid conditions are frequent occurrences among the elderly. These co-morbid conditions can cause cognitive impairment or dementia that may be treatable, such as hypothyroidism, vitamin B12 deficiencies, etc.

A basic dementia screen should be performed at the first assessment which include:

- Routine haematology e.g. full blood count and erythrocyte sedimentation rate
- Biochemistry tests (including electrolytes, calcium, glucose, and renal and liver function)
- Thyroid function tests
- Serum vitamin B12 and folate levels

NICE[13] Level III

The SIGN guidelines did not recommend any specific blood tests and indicated that these tests should be selected according to history and clinical circumstances. The Royal College of Psychiatrists in United Kingdom recommended that thyroid function test as one of the tests to be performed in patients with suspected dementia.

Both systematic reviews,[13],[63] also concluded that routine screening for syphilis was not indicated. The Singapore Guidelines stated that test for syphilis would be best done when patients exhibited clinical features of neurosyphilis.

Recommendation
Routine blood tests should be performed in those suspected with dementia. **(Grade C)**
Specific blood tests (e.g. test for syphilis) should be selected on clinical grounds according to history and clinical circumstances. **(Grade C)**

4.7 Neuroimaging

Although dementia is a clinical diagnosis, the use of neuroimaging is an important part of the evaluation of dementia. Neuroimaging encompasses both structural and functional neuroimaging.

4.7.1 Structural neuroimaging

These would include modalities such as computed tomography (CT scan) and magnetic resonance imaging (MRI) which can identify the non-neurodegenerative and potentially treatable causes of dementia. Based on the recommendations by the NICE guidelines and the SIGN, the role of structural imaging would be to rule out any intra-cerebral pathology and aid in determining the dementia subtypes. Serial MRI scanning could identify brain changes early before the clinical onset of dementia. Although not diagnostic, serial scanning can assist in clinical judgement. [13] Level I, good ;[63] 2006, Level I, good

There have been some controversies with regards to whether structural imaging should be done on all patients suspected of dementia. The Singapore guidelines suggested using the criteria of the Canadian Consensus Conference on the Assessment of Dementia (CCCAD). However, relying purely on clinical predictors for selection of patients for neuroimaging would result in a significant number of patients with reversible causes being missed. [13] ;[63];[189]

Atrophy of the medial temporal lobe structures estimated by MRI/CT Brain helps to differentiate AD from controls and AD from other dementia based on studies that used clinical diagnosis as the gold standard**.** [47] Level I, good

Subtyping of dementia can be done by using CT/MRI based on visual rating, voxel based and volumetric MRI studies of specific anatomical areas. In a cross-sectional study [190] Level III, good the white matter lesion load (WML) scores of the whole cerebrum and the frontal lobe were significantly increased in VaD as compared to cognitively normal controls, MCI and AD ($p<0.001$) even after correcting for age and cognitive performance.

Structural neuroimaging had added value in the routine clinical assessment of cognitively impaired patients and is useful for the diagnosis of all neurodegenerative dementias or VaD, but mainly of non-AD cases (AD cases-Number Needed to Test =15.3, compared to non-AD, Number Needed to Test = 4.1). However taking all dementia diagnoses into account, the use of neuroimaging yielded Number Needed to Test = 9.[191] Level III, good

A combination of neuropsychological testing and neuroimaging could benefit in the early detection of dementia and MCI. A four-year longitudinal study on healthy subjects showed that when neuropsychological testing using Weschler Memory Scale (WMS) was combined with the summed gray matter volume on MRI, the specificity increased from 75% to 92%, and was able to differentiate the presymptomatic MCI from the healthy group. Sensitivity remained at 78%. [192] Level II-2, fair

Changes in the hippocampus and/or entorhinal cortex were able to differentiate those with MCI who subsequently develop AD from those who did not progress. Imaging measures of the hippocampus could help differentiate AD (including early stage) from controls with < 6% overlap rates. [13] Level I, good

The Alzheimers Disease Neuroimaging Initiative (ADNI) is a longitudinal study that looked into using the tensor based morphometry on serial MRIs on healthy controls, MCI and AD patients. The AD group showed a significant and more generalised atrophy (rates vary from 2.1% to 2.4% in AD compared to 0.2% to 0.7% in healthy controls). The MCI converters showed a more restricted atrophy profile compared to the AD group.[193] Level II-2, good

Post-mortem studies have shown that thickness is reduced in regions of the cerebral cortex that are affected with AD.[194];[195] Methods have been developed to measure cortical thickness on MRI. Initial studies of cortical thickness had demonstrated that thinning in distributed association areas suggested that regional atrophy can be detected across widespread cortical region. A study (n=64) found that AD patients had a thinner cortex ($p < 0.001$) in parts of bilateral parietal and precuneus regions compared to FTD patients. In AD the cognitive impairment was negatively correlated with cortical thickening in the frontal, parietal and temporal lobes, while similar correlations were not significant in FTD. Measuring cortical thickness was found to be equivalent to the cortical volume in differentiating between normal ageing, AD and FTD. [196] level III, poor

A longitudinal study (n=380) compared cortical thinning to brain amyloid imaging among normal individuals and in those at different stages of dementia. The finding showed that thinning in vulnerable cortical regions was related to symptom severity even at the earliest stages of clinical symptoms. Subtle thinning was also seen in asymptomatic older controls with brain amyloid binding as detected with amyloid imaging. [197] Level II-2, good

In the local context, CT scan and high resolution and diffusion weighted MRI brain is currently available, for clearer delineation of frontal and temporal lobe atrophy, subcortical white matter changes as well as changes seen in Creutzfeld-Jakob Disease (CJD). However expertise to quantify volumetric changes is severely lacking.

Recommendation
Structural neuroimaging such as CT scan of the brain and MRI should be done where available in the evaluation of dementia to rule out intracranial pathology. **(Grade A)**
MRI is the modality of choice to assist with early diagnosis and to detect subcortical vascular changes. **(Grade C)**

4.7.2 Functional Imaging

Functional neuroimaging includes functional MRI, magnetic resonance spectroscopy (MRS), positron emission tomography (PET), single photon emission computed tomography (SPECT) and many others. Specific ligands such as the Pittsburgh Compound B (PIB) can be used with PET, as PET-amyloid imaging markers. Use of such markers is currently limited to research setting.

Functional imaging is useful to help in the early detection of dementia, to predict changes from MCI to incident dementia and also in the subtyping of dementia.

a. Single photon emission computed tomography (SPECT)

SPECT can be used to differentiate AD, VaD & FTD if the diagnosis is in doubt. SPECT imaging, iodine-123-radiolabelled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT would be useful if the diagnosis of DLB and PDD is in doubt.

A systematic review looked at the accuracy of both perfusion hexamethylpropyleneamine oxime (HMPAO) SPECT and 2(18F) fluoro-2-deoxy D-glucose PET (FDG PET) showed a Sn of 77.1% and a Sp of 89% in separating AD from normal controls, a Sn of 71% and Sp of 76% in separating AD from VaD, and Sn of 71% and Sp of 78% in separating AD from FTD. On comparing the clinical criteria (with pathological confirmation) to SPECT, the clinical criteria for AD, was more sensitive than SPECT (81% vs 74%). However, SPECT provided higher specificity against other types of dementia better than the clinical criteria (91% vs 70%).[13] Level I, good

b. Positron emission tomography (PET)

Fluoro-2-deoxy D-glucose (FDG-PET) had sensitivity and specificity of 90% and 70% respectively in pathological verification studies. It may have superiority over SPECT in detecting AD. [13];[164] Level I, good

Standardized disease specific PET patterns could classify AD (95%), DLB (92%), FTD (94%) and normals (94%). Posterior cingulate cortex and hippocampal hypometabolism was seen in MCI. An AD PET pattern was seen in 79% of MCI patients with deficits in multiple cognitive domains and 31% amnesic MCI. MCI with non-memory deficits showed patterns ranging from absent hypometabolism to FTD and DLB PET patterns. [198] Level III, good

In an eight-year cohort study of healthy elderly population using FDG-PET, the baseline hippocampal glucose metabolic rates (MRglc) predicted decline from normal to AD with 81% accuracy, from normal to other dementias with 77% accuracy, and from normal to MCI with 71% accuracy. Greater rates of hippocampal and cortical glucose metabolic rates (MRglc) reductions were found in those who were progressing to MCI or AD. [199] Level II-2, good

c. Neuroimaging biomarkers

PET imaging studies involving radioligands that bind directly to β-amyloid plaques, such as the Pittsburgh Compound-B (PIB), a thioflavin derivative had been performed. The binding of PIB to brain sections was highly correlated with total Aβ levels. [200] ;[201]

A cross sectional study using 11-C PIB-PET, showed a correlation between beta amyloid deposition with memory impairment and those diagnosed with AD. Multiple linear regression analysis showed an increased PIB binding was related to being diagnosed with AD (β: 0.6, $p < 0.001$). There was also a strong inverse relationship between episodic memory and PIB binding in amnestic MCI (r -0.6, $p<0.001$). [202] Level II-2, fair

Another study (n=69), looked at 11 C-PIB PET binding in AD, normal aging and other dementias using visual analysis. The study found marked PIB cortical binding in AD (neocortex and caudate nuclei) ($p<0.05$), but there was no cortical binding of PIB ($p<0.05$) in FTD. In the MCI group, PIB binding clustered in AD like pattern and was indistinguishable from AD subjects ($p<0.05$). In DLB, there was an increased binding similar to AD but with a significant lower degree and variable binding levels. [203], L evel III, poor

Recommendation

Functional imaging and neuroimaging markers are not recommended routinely in the diagnosis of dementia. **(Grade C)**

4.8 Electroencephalogram

There was a limited role for the use of Electroencephalogram (EEG) in the diagnosis of dementia. [13] Level I, good;[63] Level I, good There was limited evidence that either visually rated EEG or qualitative EEG helped in the diagnostic workup to differentiate AD patients from controls and other dementia disorders. [47] Level I, good The use of EEG may be considered when there is a suspicion that there is an underlying seizure disorder, Creutzfeldt-Jakob disease (CJD) or in delirium.47] Level I, good EEG in sporadic CJD had a sensitivity of 65% and specificity of 86%. [63] Level I, good

Recommendation

The use of EEG is only for selected cases where there is a suspicion of underlying seizure disorder, Creutzfeldt-Jakob disease or delirium. **(Grade A)**

4.9 Biomarkers

Biomarkers are becoming increasingly important as possible early diagnostic measures, as surrogate measures of the ongoing pathology, prognostic markers for those at risk and to monitor drug therapy. [204] Biomarkers can be detected from the brain (cerebrospinal fluid (CSF) or neuroimaging of amyloid receptors), blood, or a combination.

Of the central nervous system biomarkers, CSF β–amyloid$_{1-42}$, β-amyloid$_{1-40}$, total tau, and hyperphosphorylated tau (p-tau) have emerged as the major biomarkers of interest. In patients with AD, there were a reduced levels of CSF β-amyloid and increased levels of CSF tau.[205]

4.9.1 CSF biomarkers

Three CSF biomarkers (Aβ, tau and ptau) were highly sensitive and specific at differentiating AD from normal ageing (Sn 92%, Sp 89%), depression and certain forms of dementia, but showed a much lower specificity at differentiating other dementias such as FTD, DLB and VaD. There was evidence that the presence of 14-3-3 protein in CSF is a predictor for sporadic CJD, with reported sensitivities and specificities of above 90%. [13] Level I, good;[63] 2006, Level I, good

Using neuropathological diagnosis of AD as the gold standard, it was shown that neuritic plaques (NPs) was the only significant predictor of low $A\beta_{42}$ levels (OR 7.2 to 53.3) and high CSF-tau (OR 9.0 to 85.1). The best documentation for Braak staging of AD was the ratio of ptau/$A\beta_{42}$ with a sensitivity of 91.6% and specificity of 85.8%, making it useful as a biomarker. [206] Level II-2, poor

The tau/$A\beta_{42}$ ratio was a better at predicting MCI and mild AD compared to the ptau/$A\beta_{42}$ ratio (AUC tau/$A\beta_{42}$=0.8 vs AUC ptau/$A\beta B_{42}$=0.7). Patients with mild AD exhibited the same CSF biomarkers phenotype as the more advanced AD. [207] Level II-2, fair

In a longitudinal study, it was found that the levels of CSF $A\beta_{42}$ and tau increased over time with comparable changes in all diagnostic groups, but there was no evidence that biomarkers were sensitive as markers of disease progression. [208] Level II-2, fair

The Alzheimer Disease Neuroimaging Initiative (ADNI) study on CSF biomarkers compared ADNI cohorts against an autopsy cohort of CSF samples which had a Receiver Operating Characteristic ROC-AUC 0.9 and sensitivity for AD detection of 96.4%. The CSF biomarker signature of AD defined by $A\beta_{1-42}$ and t-tau in an autopsy confirmed AD cohort, was also found in the ADNI cohort over the period of 12 months. It detected mild AD and predicted conversion of MCI to dementia. [209] Level II-2, good

In a cross sectional study comparing CSF biomarkers and cognitive profiles of patients with AD, the levels of $A\beta_{42}$, tau and ptau in the CSF were found to affect the severity of dementia as shown by impairment of memory, mental speed and executive functions in patients with AD. [210] Level III, fair

CSF tau/$A\beta_{42}$ may be useful in discriminating between frontotemporal lobar degeneration (FTLD) and AD (Sn 78.9%, Sp 96.6%) in autopsied patients. FTLD presented with a different profile from AD.[211] Level III, poor The ptau/$A\beta_{42}$ ratios showed the best sensitivity of 77.2% and specificity of 80.7% at differentiating FTLD from AD.[212] Level II-2, fair

Combining CSF biomarkers with neuropsychological testing did not improve discrimination between AD and FTLD. However the number of subjects in this study is too small to make any definite conclusion. [211] Level III, poor

When combined with amyloid imaging, levels of CSF $A\beta_{42}$, augmented clinical methods of identifying individuals with amyloid changes. CSF tau/$A\beta_{42}$ ratio showed strong promise as preclinical biomarkers that predict dementia in cognitively normal adults. [207], Level II-2, fair

There may be other potential CSF biomarkers such as CSF serphins, Visinin Like protein-1 (VLP-1) and cytokines. The study on the latter was excluded because of poor quality. However a cross sectional study of CSF serphins and 1-antichymotrypsin may facilitate the diagnostic classification of AD (Sn 96.5% and Sp 77.8%) but it cannot improve the differentiation between AD and DLB. [213] Level III, good The neuronal injury markers, VLP-1, showed good correlation with ptau in AD patients (r=0.9) compared to control (r=0.6) and may have potential as a biomarkers in AD in future. [214] Level III, fair

4.9.2. Plasma biomarkers

a. Aβ biomarkers

Individuals with elevated plasma $A\beta_{42}$ were at increased risk of AD (OR 2.8, 95%CI 1.6 to 5.1). It was shown that plasma $A\beta_{40}$ and $A\beta_{42}$ but not the $A\beta_{42}/A\beta_{40}$ ratio, were modestly related to age among those who remained non demented over a period of time ($A\beta_{40}$ = r 0.2, p <0.001; $A\beta_{42}$= r 0.2, p <0.001; and $A\beta_{42}/A\beta_{40}$ ratio= 0.1, p <0.037). Therefore, $A\beta_{42}/A\beta_{40}$ ratio did not appear robust to be useful as a biomarker of AD. [215] Level II-2, good

In a 10-year cohort study (n= 593), the ratio of plasma $A\beta_{42}/A\beta_{40}$ showed evidence of association with conversion to MCI or AD (RR 3.1, 95%CI 1.1 to 8.3) . The rates of conversion were: 5% at 4 years (95%CI 3% to 8%); 11% at 6 years (95%CI 7% to 14%); 18% at 8 years (95%CI 12% to 24%) and 30% at 10 years.[216] Level II-2, fair

b. Genetic markers and plasma lipoproteins

In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (n=5804) it was found that subjects with APOE ε4 was associated with a more rapid cognitive decline, as measured by memory. There was a 2.5 fold difference incident dementia in the APOE ε4+ group. The APOE ε4+ group had higher plasma total cholesterol (p<0.001), higher LDL-C (p< 0.001), lower HDL-C (p<0.001), and higher plasma triglyceride (p<0.001) levels than the APOE ε4- group. However the influence of lipid levels on cognitive decline was less convincing. [217] Level II-2, fair

Apolipoprotein E (APOE) was not only a risk factor for AD, but it may also be a risk factor for DLB. Those with APOE ε4 allele and high cholesterol level had a four fold increase to develop AD among heterozygotes and 16 fold increased for homozygotes. APOE ε4 alelle also showed influence on DLB regardless of whether the cholesterol level was high or normal. [218] Level II-2, good) PDD when carefully defined was clearly not associated with APOE polymorphisms or with a distinctive plasma cholesterol profile. [219] Level II-2, fair

Recommendation
CSF biomarkers and plasma markers are not recommended in diagnosing mild cognitive impairment or dementia. **(Grade C)**
CSF biomarkers are not recommended in determining progression of mild cognitive impairment to dementia. **(Grade C)**
The use of genetic marker, APOE with or without plasma lipid, is not recommended to be used on a routine basis, and is only to be used in clinical trials. **(Grade C)**

5.0 PHARMACOLOGICAL INTERVENTIONS

Drugs should be used synergistically with psychosocial interventions to improve cognition, function, and behaviour. The cognitive enhancers include acetylcholinesterase inhibitors (AChEI) and N-methyl-D-aspartate (NMDA) receptor antagonist. Other agents considered include ginkgo, vitamin E, omega-3 fatty acid, folic acid, vitamin B and huperzine A.

Behavioural and psychological symptoms of dementia (BPSD), a common presentation in PWD can be controlled with antipsychotics, antidepressants and mood stabilisers.

Only specialists in the care of dementia (psychiatrists, neurologists, and physicians specialising in the care of the elderly) should initiate treatment. [220] Level I, good

Once treatment is initiated, patients should be regularly reviewed every 6 months. Assessment of cognition, global functioning and behaviour should be done regularly. Caregivers' view of the condition at baseline and at follow-up should be sought. [220] Level I, good

Recommendation
Only specialists in the care dementia (psychiatrists, neurologists, and geriatricians) should initiate treatment. **(Grade C)**
Caregivers should be involved in the management of patient from the beginning. **(Grade C)**

5.1 Cognitive enhancers

Cognitive enhancers involve two separate mechanisms of action. AChEI works by augmenting the levels of acetylcholine in the brain to compensate for the losses of cholinergic function. Another mechanism of action is via continuous stimulation of NMDA receptors by glutamate which triggers a cascade of biochemical events that damage and kill surrounding neurones. [221]

Acetylcholinesterase Inhibitors (AChEI) are currently recommended for mild to moderate dementia (see the classification of severity in section 4.5). However, only donepezil has been approved for severe dementia. Memantine an NMDA receptor antagonist is approved for moderately severe to severe dementia.

This section on cognitive enhancers is adapted from the NICE technology appraisal 2006. Although AChEI is recommended only to people with AD of mild to moderate severity, healthcare professionals should not rely on MMSE scores in deciding treatment initiation. [220] Level I, good

5.1.1 Alzheimer Disease

a. Mild to Moderate Alzheimer disease

Donepezil

Donepezil was found to be beneficial but of modest clinical significance in treating cognitive decline in patients with AD based on 13 published RCTs, two systematic reviews and an unpublished RCT. [220] Level I, good

Donepezil 10 mg (Weighted mean difference WMD = 3.01, 95%CI –3.9 to –2.1) was found to be more efficacious than donepezil 5 mg (WMD= -5.5, 95%CI -3.3 to–1.8) was better compared to placebo in terms of change from baseline on Alzheimer disease Assessment Scale-Cognition (ADAS-Cog). Using MMSE score, the change from baseline was better for donepezil 10 mg (WMD of 1.3, 95%, CI 0.8 to 1.8) compared to placebo.[220] Level I, good

In another RCT, donepezil improved the MMSE score on average of 0.8 point when compared to placebo (95% CI 0.5 to 1.2, $p < 0.0001$).[220] Level I, good

Donepezil had fewer adverse events (mainly nausea, vomiting, diarrhea) when compared with rivastigmine based on a large RCT (n=998). [222] Level I, good

Rivastigmine

Evidence from three systematic reviews, four published RCTs (n=1940) and two unpublished RCTs (n=1380) suggested that rivastigmine was beneficial in AD at higher doses (6–12 mg/day). [220] Level I, good

A meta-analysis of two RCTs (26 weeks duration) was associated with a significant difference (MWD=-3.1, 95%CI,-3.8 to –2.4) for rivastigmine 6–12 mg/day when compared with placebo using the ADAS-cog. [220] Level I, good

The Investigation of transdermal Exelon in Alzheimers disease (IDEAL)study (n=1195) found that rivastigmine patch, 17.4 mg (20cm^2/24 hours) and 9.5 mg (10 cm^2/24 hours) showed similar efficacy to capsule (6 mg bd). However the target dose was not achieved in most of the patients and the effective comparison dose was 9 mg/day (capsule). In this study, all rivastigmine groups compared to placebo showed statistically significant benefit at week 24 on ADAS-cog, only on the intention to treat - last observation carried forward (ITT-LOCF) analysis ($p < 0.05$). [223] Level I, good

The 9.5 mg patch had approximately two thirds fewer reports on nausea (7.2% versus 23.1%) and vomiting (6.2% versus 17%) compared to capsule. However the 17.4 mg patch had similar tolerability to capsule. Local skin tolerability was good (>90% experiencing no, slight or mild skin irritation).[223] Level I, good

Galantamine

Based on a systematic review of seven published RCTs and one unpublished RCT (total n=4300), galantamine was found to be beneficial but of modest clinical significance. [220] Level I, good

Galantamine (24 mg) when compared to placebo showed significant improvement in ADAS-Cog change from baseline (MWD= -3.3, 95%CI –3.9 to -2.7).[220] Level I, good

Head to head comparison of AChEI

In two RCTs comparing donepezil with rivastigmine, there was no statistically significant difference in terms of cognitive changes from baseline. There was no published study comparing rivastigmine with galantamine. [220] Level I, good

A Cochrane systematic review found that all three AChEI were efficacious for mild to moderate AD, with no significant differences between them. [222] Level I, good

Memantine

A Cochrane review, based on three RCTs found that memantine (20 mg/day) showed small beneficial effect on clinical impression of change (CIBIC-Plus) (CIBIC-Plus 0.13 points change, 95% CI: 0.01, 0.25, p = 0.030), and ADAS-Cog (0.99 points, 95%CI 0.2 to 1.8, p=0.01) for patients with mild to moderate AD at 24 weeks. There was no significant difference in the number of patients experiencing at least one adverse event (NNH=39). [224] Level I, good

In a RCT (n=403), memantine compared to placebo had been shown to be effective in improving cognitive function in mild to moderate AD (-1.9 points, 95%CI, -3.1 to -0.6) on the ADAS-cog at week 24 endpoint. The Mixed Model Repeated Measure analysis favoured memantine treatment at endpoint (-1.4 points, 95%CI -2.3 to -0.5, p=0.003). [225] Level I, good)

Memantine is registered to be used **only** in the treatment of moderately severe to severe AD. However in patients who are unable to tolerate AchEI, memantine may be considered as an alternative.

Recommendation
Acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine) are beneficial in improving cognitive function of people with mild to moderate Alzheimers disease. **(Grade A)**
Patients on cognitive enhancers should be reviewed at least once every 6 months by using psychometric measures (e.g. MMSE or similar, functional and behaviouralmeasures). **(Grade C)**

b. Moderately Severe to Severe Alzheimer Disease

Donepezil

A Cochrane review showed that donepezil was effective in improving cognitive function in moderate to severe AD treated for up to 52 weeks at a dose of 10 mg/day (WMD=-2.9, CI 95%, -3.6 to -2.2) on ADAS-Cog. The benefits for patients on the 10 mg/day dose were only marginally larger than those on the 5 mg/day dose. [222] 2006 Level I, good

Another RCT reported that patients treated with donepezil improved more on the Severe Impairment Battery (SIB) (Least square [LS] mean difference= 5.5, 95%CI 1.5 to 9.8, p=0.008) and declined less on the Alzheimers Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) (LS= 1.7, 95%CI 0.2 to 3.2, p=0.03). There was also improvement in the MMSE scores from baseline at 6 months after initiation of treatment when compared to controls (LS=1.4, 95%CI 0.4 to 24, p=0.009). [226] Level I, good

The incidence of adverse events was comparable between groups (donepezil 82% versus placebo 76%) with most being transient and mild or moderate in severity. More patients discontinued treatment because of adverse events in the donepezil group than in the placebo group. [226] Level I, good

Another placebo-controlled RCT had found that donepezil was superior on SIB score change from baseline to endpoint ($p< 0.0001$). The results were also in favour of donepezil in terms of CIBIC-Plus ($p < 0.0473$) and MMSE ($p< 0.0267$). [227] Level I, good

The reported adverse events were consistent with known cholinergic effects of donepezil. The safety profile of donepezil in patients with severe AD was found to be similar to those with mild to moderate AD. [227] Level I, good

Rivastigmine

There was modest benefit for moderately severe AD (MMSE 10 to 14), in terms of ADAS-Cog scores (99%CI -7.5 to -2.6) based on the manufacturer's ITT-LOCF data from trials (n=232) of up to 24 weeks. However, there was no evidence to support the use of rivastigmine in severe dementia (MMSE < 10). [220] Level I, good

Galantamine

For moderately severe AD, there were some modest benefits in terms of ADAS-Cog scores (-6.1points, 99%CI -7.9 to -4.3) based on the manufacturer's ITT-LOCF data from trials (n=340) of up to 24 weeks. [220] Level I, good

The SERAD (Safety and Efficacy of Reminyl in Alzheimers disease) study found that galantamine could be used safely in elderly patients with severe AD. Although galantamine improved cognitive function, it failed to significantly improve the co-primary parameter of overall activities of daily living. The mean total SIB score improved by 1.9 points (95%CI –0.1 to 3.9) with galantamine, and worsened by 3.0 points (95%CI –5.6 to –0.5) with placebo. The between-group mean difference was 4.4, (LS= 4.4, 95%CI 1.3 to 7.5, p=0.006). [228] Level I, good

Memantine

Memantine is effective in improving cognitive function of people with moderate to severe AD. This conclusion was based on two systematic reviews, 13 published RCTs (n=4200) and one unpublished RCT. Two RCTs (n=650) showed less deterioration of cognitive function following treatment with memantine compared with placebo as measured by the SIB. The mean change from baseline at end point LOCF analysis for memantine and placebo was –4.0 and –10.1 respectively (p < 0.001). There were however no statistically significant differences on the CIBIC, MMSE and NPI. [220] Level I, good

In a Cochrane review, treatment with memantine (20 mg/day) in patients with moderate to severe AD was found to have a small beneficial effect in two of three studies of six-month duration. The beneficial effects were on cognition using SIB (2.9 points, 95%CI 1.7 to 4.3, p < 0.00001), ADL (ADCS-ADLsev) (1.3 points, 95% CI 0.4 to 2.1, p=0.003), mood and behaviour (NPI)(2.8 points, 95%CI 0.9 to 4.6, p=0.004), and CIBIC-Plus (0.28 points, 95%CI 0.2 to 0.4, p< 0.0001). [224] Level I, good

Another placebo-controlled trial (n=350) which used SIB as an outcome measure found a significant effect at week 12 (p=0.019) and at week 18 (p=0.048) on the LOCF analysis, but failed to show any statistically significant benefit at week 24. [229] Level I, good

Recommendation
Donepezil and memantine are modestly effective in improving cognitive function of people with moderate to severe Alzheimers disease**. (Grade A)**
Galantamine may offered as an alternative in those with severe Alzheimers disease. **(Grade B)**
Patients on cognitive enhancers should be reviewed at least once every 6 months by using psychometric measures (e.g. MMSE or similar, functional and behaviouralmeasures). **(Grade C)**

5.1.2. Vascular dementia

There are well documented cholinergic deficits in VaD. [230] Ischaemia induces excessive glutamate stimulation on NMDA receptors. This leads to excitotoxicity and neuronal cell death.[230] Donepezil has been approved for VaD treatment in New Zealand, India, Romania, South Korea and Thailand, while memantine has been approved in Argentina, Brazil and Mexico.[231]

a. Cognitive enhancers

Acetylcholinesterase Inhibitors(AChEIs) and memantine are currently prescribed in dementia, other than AD, as part of a clinical trial or at clinical discretion without licence. [13] Level I, good

Their efficacy and adverse effects in VaD had been reported in a recent meta-analysis of placebo-controlled RCTs (n=5183, duration 24-28 weeks), comprising of three trials on donepezil, two on galantamine, one on rivastigmine and two on memantine. [231] Level I, good There were significant cognitive effects for all drugs using ADAS-Cog (-1.1 points, 95%CI, -2.2 to -0.1); for rivastigmine (12 mg daily), (-1.6 points, 95%CI -2.4 to -0.8) for galantamine (24 mg), (-2.2 points, 95%CI -3.0 to -1.4) for donepezil (10 mg daily) and (95%CI -2.8 to -0.9) for memantine (20 mg). On the Clinical Global Impressions scale (CGI scale), only donepezil 5 mg daily had a positive effect (OR 1.5, 95%CI 1.1 to 2.1). Donepezil (10 mg) also showed a beneficial effect on the Alzheimer Disease Functional Assessment and Change Scale (ADCS-CGIC) (-1.0 point, 95%CI, -1.7 to -0.2). There were more dropouts and adverse events (mainly gastrointestinal symptoms and insomnia) with the AChEIs, but not with memantine. [231] Level I, good

In eight systematic reviews and RCTs,[230] Level I,fair donepezil (5 mg) was found to be the most effective with a numbers needed to treat (NNT)=10, and numbers needed to harm (NNH)=50 compared to other AChEIs. Galantamine (24 mg daily) was also found to be effective (NNT=7) but less well tolerated (NNH=7). Rivastigmine was not recommended due to insufficient evidence. Memantine (20 mg daily) appeared to be safe and well tolerated but did not demonstrate effectiveness across all cognitive outcomes and clinical global measures (NNT= 30). There was significantly less agitation with memantine treatment than with placebo (OR=0.5, 95%CI 0.31 to 1.0; NNT=30, 95%CI 15-337). [230] Level I, fair

In a placebo-controlled RCT of CADASIL patients (n=168, 18-week duration), donepezil (10 mg) was found to have no treatment effect on the primary endpoint, the Vascular-ADAS-cog. However, there was significant treatment effect favouring donepezil on the following secondary outcomes involving executive function tests: Trail Making Test (TMT) B Time (p= 0.023), TMT A Time (p= 0.015), and executive interview-25 item (EXIT25) (p= 0.022). [12] Level I, good

Although the improvements were noted on several measures of executive function and processing speed, the clinical relevance of these findings was not clear as the improvements did not translate into a clinical meaningful benefit on IADL and on global dementia rating such as Disability Assessment for Dementia (DAD) and CDR-SB. [12] Level I, good)

Recommendation

Acetylcholinesterase inhibitors may be prescribed in selected patients with vascular dementia at the clinician's discretion. **(Grade A)**

b. Drugs that control vascular risk factors

For people with VaD, there is currently no evidence to suggest that drugs that control vascular risk factors such as anti-hypertensive, aspirin, statin and antidiabetic have any beneficial effect on cognitive symptoms. [232] Level I, good It is assumed that the control of these comorbid conditions reduces the risk of further cerebral damage, but there is no direct evidence that there will be any beneficial effect on cognitive function. [13] Level I, good)

Recommendation

Patients with vascular dementia with concurrent vascular risk factors should be treated with recommended drugs for the management of these problems. **(Grade C)**

5.1.3. Lewy Body Diseases (Dementia with Lewy Body/Parkinson Disease Dementia)

There is current interest in the overlap between PDD and DLB. Both conditions have common presentations, involving similar brain areas, and both are associated with deficits in both acetylcholine and dopamine. At present there is no agent that slows down the progression of PDD.[13] Level I, good These groups of degenerative dementias are associated with prominent BPSD, but the use of neuroleptics lead to two to three fold increase in mortality due to severe neuroleptic sensitivity reactions. [233] Unfortunately, there had been too few studies focusing on the use of AChEIs in the treatment of these conditions.

Rivastigmine is licensed for the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson disease and DLB.[13] Level I, good)

A large RCT of rivastigmine in PDD, showed improvement in primary and secondary endpoints. However, the clinical significance of these benefits were uncertain. It was likely that the modest improvements reflected heterogeneity of response, with some patients responding far better than others.[13] Level I, good

A systematic review found that there was evidence from one RCT (n=541) that rivastigmine had a moderate effect on cognition and to a lesser extent on ADL in patients with PDD. The LOCF change score from baseline to week 24 significantly favoured rivastigmine: ADCS-CGIC, ((WMD=-0.50, 95% CI -0.8 to -0.2, p=0.0004); MMSE (WMD=2.8, 95% CI 0.3 to 1.7, p=0.003); ADAS-Cog (p=0.0002) and ADCS-ADL (WMD= 2.5, 95% CI 0.4 to 4.6, p=0.02). [234] Level I, good

Clinically moderate or marked improvement on cognition and ADL were observed in 19.8% of the rivastigmine group and 14.5% of the placebo group (NNT=19); whereas clinical worsening was observed in 13.0% and 23.1%, respectively. Overall, rivastigmine had moderate effect on cognition and to a lesser extent on ADL.[234] Level I good

Tolerability issues such as nausea and vomiting (NNH=11) appear significant and will require careful management. More patients on rivastigmine compared to placebo experienced nausea (NNH=6), vomiting (NNH=7), tremor (NNH=16) or dizziness (NNH=22).[234] Level I, good

A Cochrane systematic review on DLB, found no statistically significant difference between rivastigmine and placebo at 20 weeks (WMD=1.2, 95%CI, -0.6 to 3.0, p=0.19).[14] Level I, good

Recommendation
Rivastigmine may be considered in improving cognition in Lewy Body Dementias. **(Grade A)**
Rivastigmine should be used cautiously in patients with Parkinson Disease Dementia. **(Grade A)**

5.1.4 Frontotemporal Dementia (FTD)

The clinical and pathologic heterogeneity of frontotemporal lobar degeneration (FTLD) creates particular challenges for determining optimal pharmacologic management. Unlike AD, cholinergic neurons are relatively preserved in FTD, and studies using AChEIs have produced mixed results.

There had been reports that AChEIs frequently lead to more severe behavioural impairments. [24];[174] A number of other medications that affect the function of specific neurotransmitter systems (example: SSRI on serotonergic neurons; memantine on the aberrant glutamatergic neurotransmission) have been studied and may offer modest benefits for the behaviouraland cognitive sequelae of this disorder. [235] There are no approved treatments available for any of the FTLD syndromes.

a. Acetylcholinesterase inhibitors

There had not been many trials of AChEIs in FTLD, as there was no rationale for using medications that increase brain acetylcholine in patients with FTD. In a study of FTD patients (n=24) who were treated with donepezil (10 mg, 6 months), against those not treated, there was an increased of disinhibited or compulsive acts on the FTD Inventory scores (p=0.05) in 30% of the subjects. There was no change in the global cognitive performance or severity of dementia in the donepezil group. Even though the number of subjects was small, the findings indicated that AChEIs could worsen disinhibition and compulsions in patients with FTD.[174] Level III, poor

An open label placebo-controlled RCT (18 weeks open-label and 8 weeks of placebo RCT) of galantamine (16–24 mg) did not find any significant differences in the primary efficacy measures using the Clinical Global Impression of Improvement (CGI-I) and Clinical Global Impression of Severity (CGI-S). There was also no significant difference found on behaviour using the Frontal Battery Inventory. The frequency of adverse events was more than 10%, but no significant differences were observed in the two groups. [236] Level I, poor

b. Memantine

There is no placebo RCT available. A 26-week (n=37), open-label study of memantine (20 mg daily) showed that Semantic Dementia (SD) and FTD patients had greater decline on the ADAS-Cog (SD subjects, p=0.001; FTD subjects, (p=0.156). MMSE declined significantly (p=0.002) in the FTLD combined. The overall change in CDR-SOB, was not significant (p=0.24). Effects on behavior showed a transient improvement on NPI score, maximal at week 16, but back to baseline by week 26. This was most prominent in the FTD group. The overall estimate of change on the Frontal Battery instrument (FBI) at week 26 was 2.4±1.2 points (p=0.038). The most common side effect was confusion.[24] Level III, fair

Recommendation
Acetycholinesterase inhibitors are not recommended for the treatment of frontotemporal dementia**. (Grade A)**
Memantine is not recommended for frontotemporal dementia. **(Grade C)**

5.1.5 Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is a heterogeneous clinical condition with several subtypes and multiple aetiologies.[237];[83] There are still controversies on the use of cognitive enhancers in the treatment of MCI.

a. Galantamine

A Cochrane systematic review of two placebo controlled RCT (n=1903) found no significant treatment effect on the ADAS-Cog at 12 months (WMD= -0.1, 95%CI -0.6 to 0.4) or 24 months (WMD=1.5, 95% CI, 0.9 to 2.4). One of the trials reached significance in terms of conversion to dementia (change of CDR score from 0.5 to ≥1.0) at 24 months. Combining data from both trials, dementia conversion at 24 months was significant (OR 0.7, 95%CI 0.6 to 0.9) for galantamine (12-24 mg).[238] Level I, good

A significantly higher death rate however was found in the galantamine group. Causes of death included bronchial carcinoma/sudden death, cerebrovascular disorder/syncope, myocardial infarct and suicide. An interim study from the manufacturer reported an adjusted HR of 3.0 (95%CI 1.3 to 7.3). This review concluded that there was some marginal clinical benefit, but as yet unexplained excess in death rate.[238] Level I, good

A consensus statement by the British Association for Psychopharmacology reported that a significantly increased mortality in two unpublished studies of galantamine have been observed and remain to be explained.[239] Level III, good

b. Donepezil

A Cochrane review based on two RCTs (n=782), reported no evidence to support the use of donepezil in MCI patients. This review concluded that the putative benefits are minor and short lived. Those on donepezil suffered significantly more side effects, mainly gastrointestinal and were dose related.[240] Level I, good

One of the RCTs demonstrated a modest treatment effect with donepezil (10 mg/day) compared with placebo at 24 weeks, on the ADAS-Cog (MD=1.9, 95%CI 0.5 to 3.3, p=0.007), using the ITT-LOCF analysis. There were no significant treatment effects for donepezil compared with placebo for other measures of cognitive function. In the second study, there was a significant difference in the donepezil group (NNT=12, OR 0.4, 95%CI 0.2 to 0.7, p=0.003), after the first year of treatment. However this difference was not significant at the end of 3 years (OR 0.8, 95%CI 0.6 to 1.3, p=0.4).[240] Level I, good

In a more recent double-blind placebo controlled RCT (n=821) of MCI with a three-week placebo run-in followed by 48 weeks of donapezil, there was a small but significant decrease in modified ADAS-Cog scores in favour of donepezil. Little change from baseline in CDR-SB was observed in either group. Using the CGI of Change, the donepezil treated group scored better only at week 6 (p=0.04).[241] Level I, good

Adverse events were generally mild or moderate. More donepezil treated subjects (18.4%) discontinued treatment due to adverse events than placebo-treated subjects (8.3%). The most frequent adverse events leading to discontinuation of donepezil were diarrhoea (16.4%), muscle spasm (13.3%) and nausea (9.7%).[241] Level I, good

c. Rivastigmine

A placebo-controlled RCT (n=1018) concluded that there was no significant benefit of rivastigmine on the progression rate to AD or on cognitive function over four years. It was found that 17.3% of patients on rivastigmine and 21.4% on placebo progressed to AD (HR = 0.8, 95%CI 0.6 to 1.1, p=0.225). There was no significant difference between the rivastigmine and placebo groups on the cognitive test battery.[223] Level I, fair

Similar adverse events were reported for rivastigmine (95.6%) and placebo (92.7%). The frequencies of nausea, vomiting, diarrhoea, and dizziness were two to four times higher in the rivastigmine group. Most adverse events were mild or moderate in both groups. [223] Level I, fair

Recommendation
Acetylcholinesteras inhibitors are not recommended in people with mild cognitive impairment. (**Grade A)**

5.2. DRUGS TO CONTROL BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)

The management of BPSD is challenging. Concerns have been raised in identifying which behaviours and which patients are most likely to improve. Although non-pharmacological interventions should be the first-line treatment, a wide variety of pharmacological agents can be used synergistically in the management of BPSD.

5.2.1. Treatment of Agitation, Aggression and Psychosis

a. Antipsychotics

Antipsychotic drugs are the most frequently used 'off-label' for institutionalized patients with dementia.[242] In the US and Europe, up to 60% of people with dementia residing in care facilities are prescribed neuroleptics.[243], Level III, fair The US Food and Drug Administration has put out black box warning about the risk of increased mortality and stroke associated with antipsychotics.[244] Level III, fair

The NICE guideline found that there is insufficient evidence to support use of atypical antipsychotics in treatment of psychosis, aggression and agitation in patients with dementia.[13] Level I, good

In a meta-analysis of 16 RCTs (n=5110) on effects of atypical antipsychotics (risperidone, quetiapine, olanzapine and aripiprazole) on agitation and aggression in dementia, the NNT ranged from 5 to 14. Small statistical effect sizes on symptom rating scales supported the evidence for the efficacy of aripiprazole, using the NPI-total (OR =1.5. 95%CI 1.1 to 2.0, p=0.005) and risperidone, using the BEHAVE-AD (OR= 1.8, 95%CI 1.4 to 2.3, p<0.0001). Meanwhile, the NNH ranged from 10 for somnolence to 100 for death. Approximately one-third dropped out without overall differences between drug and placebo (OR =1.1, 95%CI 0.9 to 1.3, p=0.5). [332] level I,fair

In the Clinical Antipsychotic Trials of Intervention Effectiveness: Alzheimers Disease (CATIE-AD) (n=421), atypical antipsychotics (olanzapine, quetiapine and risperidone) when used for psychosis or agitation/aggression were no better than placebo for the primary outcome (time to discontinuation for any reason) or the secondary outcome (CGI).The time to the discontinuation of treatment for any reason was not significant (p=0.52) for olanzapine (median 8.1 weeks), quetiapine (median 5.3 weeks), risperidone (median 7.4 weeks) and placebo (median 8.0 weeks). The median time to the discontinuation of treatment due to a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) compared to quetiapine (9.1 weeks) and placebo (9.0 weeks) (p = 0.002). However, the trial utilised a population of patients with mild agitation or psychosis. [245] Level I, fair

In the last few years, two serious adverse events have been associated with atypical antipsychotics, that is, cardiovascular events and death.[246] In the meta-analysis by Schneider *et al*, the pooled rates of cardiovascular events were 1.9% in atypical antipsychotic group versus 0.9% in placebo group (OR= 2.1, 95% CI 1.2 to 3.8).[245] Level I, fair

The DART-AD Trial (n=165) concluded that withdrawal of neuroleptics in AD patients showed no overall detrimental effect on function and cognitive status. There was no significant difference in SIB scores at baseline and at 6 months. The estimated mean difference in deterioration was favoring placebo (MD=-0.4, 95%CI -6.4 to 5.5, p=0.9). Similarly, there was no significant difference between the placebo group and the continuing treatment group (MD=-2.4,95%CI -8.2 to 3.5, p=0.4) on the NPI.[247] Level I, fair

Risperidone

In the treatment of non-cognitive functions in PWD, risperidone (mean 1 mg/day) showed improvement in neuropsychiatric symptoms as measured by NPI total and BEHAVE-AD on the psychosis (p=0.01) and aggression (p=0.0002) subscales.[242] Level I, good

An observational study (n=132) showed that risperidone was significant (p<0.0001) in improving BEHAVE-AD scores at four and 12 weeks and on most of the NPI items (p<0.0001). Agitation improved significantly (p<0.0001) at endpoint. In addition, caregiver distress was reduced significantly.[248] Level II-3 ,good

In patients with severe dementia (n=119) (MMSE 5-9), treatment with risperidone (mean 1 mg/day) showed better global improvement as measured on the CGI-C (p=0.024).[249] Level I, fair

Risperidone (all doses pooled) treated patients were significantly more likely to have serious adverse cerebrovascular events (NNH=50), falls (NNH=8) and extrapyramidal symptoms (NNH=11). [242] Level I, good

A meta-analysis (n=1721) showed that mortality associated with cardiac-related adverse events was higher with risperidone than placebo during and within 30 days of treatment discontinuation (HR 3.0, 95%CI 0.9 to 0.6) (NNH=115). Four subjects on risperidone died due to cerebrovascular events during or within 30 days of use (HR 2.7, 95%CI 0.3 to 24.0).[250] Level I, fair

Aripiprazole

Based on two RCTs (n=464), there was a moderate to high quality evidence that aripiprazole (15 mg/day for 10 weeks) produced small benefits in terms of reduced neuropsychiatric symptoms as measured by the total score on the NPI or BEHAVE-AD, in AD.[13] Level I, good

A Cochrane systematic review concluded that aripiprazole (2-15 mg) given for 10 weeks showed benefit compared to placebo, in the BPRS-Psychosis (MD=-0.7, 95%CI -1.3 to -0.1, p=0.03).[242] Level I, good

In another RCT (n=473), aripiprazole (10 mg) compared to placebo showed significantly greater improvement in mean change on the NPI-NH psychosis subscale (p=0.013 from week 6 onwards), Cohen-Mansfield Agitation Inventory (CMAI) (p=0.023) and BPRS total (p=0.030).[249] Level I, fair)

Adverse effects due to aripiprazole (2-15 mg) compared with placebo was mainly somnolence (NNH=15).[242] The cerebrovascular adverse events reported were dose-dependent ($p \leq 0.03$).[249] Level I, fair

While a study by Mintzer *et al* [249] showed improvement on the NPI-NH psychosis subscale, another study (n=256) using the same scale (p=0.883) did not find any improvement.[251] Level I, poor However, there were no long term studies on aripiprazole.

Quetiapine

The NICE Guideline concluded that quetiapine (50-100 mg/day) can be used for the non-cognitive symptoms of dementia.[13] Level I, good In a RCT (n=435) of 10 weeks duration, quetiapine (200 mg/day) improved agitation. The difference was significant on the observation carried forward (OC) analysis (p=0.014) but not on the LOCF analysis (p=0.065). In the secondary analysis, quetiapine showed significantly greater improvement on the CGI-C score compared to the placebo group on both LOCF (p=0.017) and OC (p=0.002) analyses.[252] Level I, poor

Neither quetiapine (100 mg) nor haloperidol (2.5 mg) (n=284) compared to placebo was efficacious in the treatment of psychosis using the mean total BPRS scores (p=0.217 versus placebo and p=0.354 versus haloperidol).[253] Level I, poor

There was no difference in rates of adverse events (falls, hypotension, sedation, extrapyramidal symptoms and cardiovascular adverse events between quetiapine at doses of 100 mg/day and 200 mg/day, suggesting an absence of dose-dependency for tolerability and safety. The RR for death on quetiapine versus placebo was 2.1 (95%CI 0.6 to 7.2) and was not significant.[252] Level I, poor

Olanzapine

A 24-month, open-label uncontrolled study (n=68) of olanzapine (mean dose 4 mg/day), supported the use of these medications in AD, VaD, FTD, DLB and PDD. The FTD group, showed the best response as reflected by a decrease in NPI score ($p<0.01$) and BEHAVE-AD score ($p<0.05$). In this group, the most common adverse effect was somnolence (31%), which was reduced up to 12% when the dosage was lowered. Maximal response was found among patients who presented with symptoms of delusions, hallucinations, anxiety and agitation. Benefits were also seen in the DLB group, reduced NPI score ($p<0.01$) and BEHAVE-AD ($p<0.01$). PDD patients responded well to olanzapine as seen by decreasing NPI and BEHAVE-AD scores ($p<0.05$) and ($p<0.01$) respectively. [254] Level II-3, fair

General Principles of the use of antipsychotics in BPSD

Drugs may be appropriate in the following situations:

a. Where drugs have a specific indication (e.g. depression or psychosis), regardless of the severity and frequency of symptoms

b. Where the problem symptom is severe and treatment is needed quickly e.g. dangerous or distressing to the patient or others

c. Where behaviours have no clear situational trigger or occur in a setting where carers cannot cope with serious behaviour problems

Drugs are inappropriate in these conditions: wandering, restlessness and agitated behaviours that **do not** represent a danger to the patient or others

In cases of unexpected harmful behaviours, prescription of medication on a prn (when necessary) basis is allowed. However, medication should be given not more than twice in 7 days without an assessment of the cause and development of an appropriate care plan.

For those who require regular medication, the '3T' approach is a good practice:

- drug treatments should have a specific **target** symptom
- the starting dose should be low and then **titrated** upwards and
- drug treatments should be **time limited**

Atypical antipsychotics should be continued for

- ❖ people who still have continuing BPSD
- ❖ where it is felt that severe adverse consequences may occur (or have occurred) if they are discontinued, and
- ❖ when no alternative treatment approaches are suitable.

Modified from Faculty of the Psychiatry of Old Age (2004) and the Omnibus Budget Reconciliation Act (OBRA) guidelines[255]

Recommendation

Antipsychotics should not be used routinely to treat patients with dementia with aggression and psychosis. **(Grade A)**

If indicated, atypical antipsychotics should be considered. **(Grade A)**

The family needs to be informed of the adverse events prior to commencement of treatment. **(Grade C)**

Patient should be assessed regularly and antipsychotics should be tailed down and withdrawn as early as possible, after resolution of symptoms. **(Grade C)**

Refer to Appendix 10 for drug dosages and adverse effects.

b. Cognitive enhancers

According to the NICE guideline, donepezil (10 mg/day) compared to placebo reduced neuropsychiatric symptoms in patients with dementia. There was moderate quality evidence suggesting that rivastigmine (12 mg/day for 20 weeks) may produce benefits in reducing psychotic symptoms in DLB patients. There was insufficient evidence to determine whether memantine or galantamine produce benefits in neuropsychiatric symptoms in people with VaD.[13] Level I, good

A RCT (n=262), the Cholinesterase Inhibitor and Atypical Neuroleptic in the Management of Agitation in AD (CALM-AD) concluded that the donepezil (10 mg) given for 12 weeks duration was not superior to placebo in treatment of severe agitation in patients with AD. In this study, patients had also received four weeks of psychosocial intervention prior to commencement of drugs. The CMAI score from baseline to 12 weeks did not differ significantly between the donepezil and placebo groups (MD= -0.1, 95%CI -4.4 to 4.2, p=0.94). The proportion of patients responding to treatment was similar in the two groups. The reduction in the NPI score also did not differ significantly between the two groups (p=0.96).[256] Level I, fair

A pooled post hoc analysis of six RCTs (n=1826, moderate to severe dementia) of 24/28 weeks duration, compared memantine (20 mg/day) to placebo. The ITT-LOCF analysis found that memantine treated group showed symptom improvement on the NPI total scores (p=0.008) at end-point. There was significant symptom improvement on delusions (p=0.045), agitation/ aggression (p=0.028) and irritability/lability (p=0.048). Patients who were asymptomatic at baseline also showed significantly less emergence of symptoms of agitation/aggression (p=0.002), irritability/labilty (p=0.004) and night-time behavior (p=0.050).[257] Level I, fair

A systematic meta-analysis of 5 placebo-controlled RCTs (n=1750) that rated BPSD with the NPI found that patients on memantine improved by 1.99 points on the NPI scale (95%CI -0.1 to -3.9, p=0.041). However the effect sizes were small and the studies were too heterogenous to be conclusive. [258] Level I, poor

Recommendation
Acetylcholinesterase inhibitors or memantine may be used for the treatment of behavioural and psychological symptoms of dementia. (**Grade B**)
Rivastigmine may be used in the treatment of behavioural and psychological symptoms of Lewy Body Dementia. **(Grade A)**

c. Antidepressants

In a systematic review (24 studies) on FTD, two placebo controlled RCTs using serotonergic agents were identified. The first RCT reported that treatment with paroxetine (40 mg) (n=10) for six weeks did not improve behavioural symptoms, and was associated with a worsening of cognition compared to placebo. The second RCT (n=26), was a crossover study that demonstrated a significant decrease in the NPI score with trazodone (up to 300 mg/day), but no effect was seen on the cognition (MMSE). In the same paper, a total of six open label and uncontrolled studies found that the combined mean reduction based on NPI was15.4 points with antidepressant treatment. However these studies had small sample size, most were not controlled and thus subject to placebo bias. There was likely a publication bias toward positive trials. Only trazodone appeared to have a significant effect on the behavioural symptoms of FTD.[259] Level I, fair

Recommendation

Antidepressant is not effective in the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD) in Frontotemporal dementia. **(Grade B)**

5.3 TREATMENT OF DEPRESSION AND MOOD SYMPTOMS

5.3.1 Antidepressants

Based on one systematic review which included Selective Serotonin Reuptake Inhibitor (SSRIs) and Tricycyclic antidepressants (TCAs), antidepressants were beneficial in reducing depressive episodes and improving general functioning. [13] Level I, good

A meta-analysis of five placebo controlled RCTs which included SSRIs (fluoxetine, sertraline) and TCAs (clomipramine, imipramine) showed efficacy on antidepressants in depressed AD patients (NNT=5). The NNH for dropout owing to adverse events was not statistically significant (NNH=36). Only two studies investigated the properties of the more commonly used SSRIs and no studies investigated the properties of newer classes of antidepressants.[260] Level I, fair

Recommendation

Antidepressant (preferably Selective Serotonin Reuptake Inhibitor) can be used for the treatment of depression in dementia. **(Grade A)**

Refer to Appendix 11 for drug dosages and side effects

5.3.2 Mood stabilisers

The NICE Guidelines concluded that neither valproate nor carbamazepine was recommended for use in treatment of depression or anxiety due to the significant risks that outweighed benefits. Their use is associated with more numbers of adverse events compared to placebo. [13] Level I, good

A placebo controlled RCT (n=14) concluded that valproate was not effective for the management of agitation in moderate to severe AD, and may be poorly tolerated in this population. [261] Level I, poor

Recommendation

Mood stabilisers are not recommended for mood symptoms in dementia. **(Grade B)**

5.4 COMBINATION THERAPY

As the two classes of drug (AChEI and NMDA antagonist) are believed to work on different mechanisms, it seems reasonable that additive effects can be achieved from combination therapy.

Hypofunction of other neuronal systems such as monoaminergic and serotonergic systems in the brain of AD patients has also been reported. [262]

5.4.1 Combination of Acetylcholinesterase Inhibitor with memantine

In a placebo-controlled RCT (n=404), subjects with moderate to severe dementia on donepezil therapy were randomised to receive memantine or placebo. The result favoured the combination of donepezil with memantine as seen in the small but significant effects on global function, (55% vs 45% unchanged/improved on CIBIC), cognitive function (SIB 3.4 points), ADL and BPSD (NPI 3.8 points). [13] Level I, good

In a prospective non-randomised trial (n=382) the combination of memantine and AChEI slowed the cognitive ($p<0.001$) and functional decline ($p<0.001$) in AD, compared to AChEI alone or no treatment. [263] Level II-2, poor

Another prospective non-randomised trial (n=202) in moderate to severe dementia, showed that combining AChEI with memantine had beneficial effect in terms of cognitive function compared to monotherapy (77.9% versus 46.3% respectively). [264] Level II-2, poor

5.4.2 Combining Acetylcholinesterase Inhibitor with Selective Serotonin Reuptake Inhibitor (Serotonin Augmentation)

A RCT (n=122) did not show any superiority of adding serotonin stimulation to rivastigmine in improving cognitive function using MMSE (p=0.002) and Weschler Memory Scale III (p=0.00) compared to rivastigmine alone on the MMSE (p=0.000) and WMS-III (p=0.000). [265] Level I, fair

5.4.3 Combining Acetylcholinesterase Inhibitor with multivitamin supplementation

A placebo-controlled RCT (n=89) combining multivitamin supplement (vitamin B6, B12 and folic acid) to donepezil in patients with dementia, found no beneficial effects on cognition (ADAS-Cog, p=0.34; MMSE, p=0.79) and ADL (Cognitive Abilities Screening Test [CASI], p=0.51; ADL, p=0.70; IADL, p=0.89) [266] Level I, fair

5.4.4 Combining Acetylcholinesterase Inhibitor with non pharmacological intervention

The NICE guideline, based on four RCTs concluded that there was a significant treatment advantage on the cognitive symptoms using MMSE, when AChEI was combined with cognitive stimulation. [13] Level I, good

In an open label study (n=24), patients who were already on AChEI, had some additional benefit with the utilsation of multisensory behavioural therapy (MSBT) in addition to standard psychiatric inpatient care. This study showed that this combination may reduce apathy and agitation (p=0.04) and additionally improve ADL (p=0.04). [267] Level II-1, poor

Combining donepezil and psychosocial intervention was noted to increase positive effect of quality of life when compared with donepezil alone (n=28, p=0.007). [268] Level II-1, poor

Recommendation
Adding memantine to acetylcholinesterase inhibitors in moderate to severe Alzheimers disease may be of benefit. **(Grade B)**
Combining acetylcholinesterase inhibitors with non-pharmacological intervention may be of benefit in patients with dementia. **(Grade B)**

5.5 ALTERNATIVE/COMPLEMENTARY MEDICATION

A number of other alternative or complementary preparations have been suggested or investigated in the treatment of dementia. This CPG will review the evidence on these preparations.

5.5.1 Ginkgo biloba

Ginkgo biloba is widely available and, is marketed for 'cerebral insufficiency'. There are many different agents of the extract. The potential mechanisms of action include vasoactive effects, antiplatelet activity, increasing neuron tolerance to anoxia and prevention of membrane damage caused by free radicals.[13] Level I, good

The NICE guideline concluded from one systematic review (33 placebo-controlled RCTs, n=3,278) of ginkgo biloba (80 to 600 mg/day for 3 to 52 weeks) and one new RCT (n=123) of ginkgo (160 to 240 mg/day) that the benefits of ginkgo may outweigh adverse events.[13] Level I, good

A Cochrane systematic review of 35 placebo-controlled RCTs (n=4247) of ginkgo biloba (120 mg to 240 mg/day) appeared to be safe with no excess adverse effects. The evidence that Ginkgo biloba had predictable and clinically significant benefit for PWD or cognitive impairment was inconsistent and unconvincing.[269] Level I, good

Two trials (n=783) on the ADAS-Cog showed no significant difference (p=0.7) between ginkgo biloba and placebo. However, four trials using the Syndrom Kurz Test (SKT), noted a significant difference in favour of Ginkgo biloba for the low dose (MD= -3.1, 95%CI -4.0 to -2.2, p<0.00001, two studies) and high dose (MD=-3.6, 95%CI -3.9 to -3.1, p<0.00001, three studies), and all doses pooled (MD=-3.6, 95% CI -3.9 to -3.2, p<0.00001, four studies).[269] Level I, good

Two RCTs (n=549) using the Clinical Global Impression of Change (CGIC) scale showed benefits associated with ginkgo (>200 mg/day) at 24 weeks (NNT=10). However, another two RCTs (n=652) showed no benefit with the lower dose (< 200 mg/day) (OR=1.7, CI 0.9 to 1.7, P=0.2).[269] , Level I, good

Using the Sandoz Clinical Assessment Geriatric Scale (SCAG) there was benefit with ginkgo (< 200 mg/day) compared with placebo at < 12 weeks (MD= -14.70, 95%CI -28.0 to -1.4, p=0.03, n=70), and at 12 weeks (MD= -22.2, 95%CI -29.4 to -15.0, p<0.00001, n=38). The result from one study using the Crichton Rating Scale showed benefit for ginkgo (< 200 mg/day) compared with placebo at 12 weeks (MD= -5.0, 95% CI -7.9 to -2.1, p=0.0007).[269] Level I, good

Ginkgo causes bleeding when combined with warfarin or aspirin, raises blood pressure when combined with a thiazide diuretic and possibly causes coma when combined with trazodone.[270]

Recommendation
Ginkgo Biloba is not recommended for the treatment of dementia. **(Grade A)**

5.5.2 Omega-3 fatty acid

Several epidemiologic studies showed a protective effect with increase fish consumption. The data indicated a beneficial effect of omega-3 or commonly known as fish oil on the preservation of cognition in AD.[271]

Two placebo-controlled RCTs found that omega-3 fatty acid did not show any effect on the cognitive function (p=0.40) in patients with mild to moderate AD. However both RCTs showed positive effects in a small group of patients with very mild AD (MMSE>27, p=0.01) and MCI (p=0.03).[272] Level I, poor;[271] Level I, good

The decline in MMSE was not significant (p=0.4) during the first six months (–1.0 point for omega-3 [4 gm daily] versus –1.4 points in the placebo group). In patients with more advanced AD, the decline rate tended to be more rapid in the omega-3 group than in the placebo arm, (–0.9 vs 0 point, p=0.15). In the very mild AD group, there was no significant treatment effect (p=0.96) for the ADAS-Cog scores over time.[271] Level I, good

Recommendation
Omega -3 should not be used in the treatment of dementia**. (Grade A)**

5.5.3 Folic acid and Vitamin B

Individuals with AD have been found to have higher plasma homocysteine level than age matched control. It has been reported that elevation of plasma homocysteine levels precedes the clinical manifestation of AD. Folic acid supplementation causes a significant decline in blood total homocysteine levels. Many studies are in progress to assess the effects of reducing homocysteine levels by the clinical manifestation of AD. Folic acid supplementation causes a significant decline in blood total homocysteine dietary supplements of folic acid alone or in combination with B12 and B6. [51]

The NICE guidelines concluded that folic acid (2 to 15 mg/day, for 1 to 3 months) had an increased risk of adverse events and this outweighed any potential benefit. In addition there was insufficient evidence for vitamin B12 treatment for up to five months.[13] Level I, good

A placebo controlled RCT of 18 months duration with high dose vitamin supplements (5 mg/day of folic acid, 1 mg/day of vitamin B12, and 25 mg/day of vitamin B6) concluded that these supplements did not slow cognitive decline in individuals with mild to moderate AD. The ADAS-cog score did not differ between treatment groups (p=0.52). There was an excess number of adverse events especially depression in the high-dose group (NNH=10) (p=0.02).[273] Level I, good

A recent systematic review of eight placebo controlled RCTs (four trials of healthy older people and four with mild to moderate dementia) with or without folate deficiency, concluded that there was no consistent evidence that folic acid alone or in combination with vitamin B12 had any effect on cognitive function (MMSE, WMD=0.4, 95% CI -0.4 to 1.2, p=0.35; ADAS-Cog scales, WMD=0.4, 95%CI -1.3 to 2.1, p=0.63 and Bristol Activity of Daily Living, (WMD=0.6, 95%CI -2.0 to 0.8, p=0.42).[51] Level I, good

Recommendation

Folic acid and vitamin B are not recommended in the treatment of dementia. **(Grade A)**

5.5.4 Vitamin E

NICE guidelines concluded that vitamin E (2,000 IU total daily dose) had more risk of adverse events than benefit in people with dementia. [13] Level I, good

A recent Cochrane systematic review of two placebo controlled trials with vitamin E (2000 IU total daily dose) showed some benefits from Vitamin E with fewer participants reaching any of these endpoints: death, institutionalisation, loss of two out of three basic ADL or decline of global CDR from 2 to 3 (OR= 0.5, 95%CI 0.3 to 1.0, NNT=6). However, more patients taking Vitamin E suffered falls (OR=3.1, 95%CI 1.1 to 8.6, NNH= 3). This systematic review concluded that there was no evidence of efficacy of Vitamin E in the treatment of people with AD or MCI.[79] Level I, good

Recommendation

Vitamin E is not recommended in the treatment of dementia and mild cognitive impairment. **(Grade A)**

5.5.5 Huperzine A

Huperzine A, (derived from a Chinese club moss Huperzia serrata) is a linearly competitive, reversible inhibitor of acetyl cholinesterase. It has both central and peripheral activity with the ability to protect cells against hydrogen peroxide, beta-amyloid protein, glutamate, ischemia and staurosporine-induced cytotoxicity and apoptosis. Animal and human studies have shown Huperzine A to be a promising agent for treating acetylcholine deficit dementia including AD. [274]

A Cochrane systematic review of six RCTs (n=454) showed that Huperzine A may have some positive effects on cognitive function, global clinical status, behavioural disturbance and functional performance, with no obvious serious adverse events for patients with AD.[274] Level I, fair)

Four placebo controlled RCTs (n=220) with a dose of 0.3 to 0.4 mg daily up to 36 weeks, demonstrated a beneficial effect in the cognitive function using MMSE in AD patients (WMD=2.8, 95%CI 1.9 to 3.8, $p < 0.00001$). In the review, Huperzine A was also superior to placebo in ADL (WMD= -7.2, 95%CI -9.1 to -5.2, $p < 0.00001$). The adverse events of Huperzine A were mild and there were no significant differences of adverse events.[274] Level I, fair

A RCT (n=202) comparing Huperzine A (0.4 mg daily) with Vitamin E (200 mg daily) versus placebo plus Vitamin E (200 mg daily) showed improvement on the ADAS-Cog at six weeks (95%CI -5.2 to -2.3) and 12 weeks (95%CI -7.1 to -3.6). Due to the low methodological quality of the included trials, it was concluded that there was insufficient evidence to recommend Huperzine A.[274] Level I, fair

Recommendation
Huperzine A is not recommended in the treatment of dementia. **(Grade A)**

6.0 NON-PHARMACOLOGICAL TREATMENT OF DEMENTIA

The aim of non-pharmacological treatment or psychosocial intervention is to enhance the person's self and quality of life. There is no single optimal psychosocial approach available, and thus a multi-dimensional approach is essential to ensure effective interventions. This approach should be person-centred and has to be individualised and tailored to the person's needs, personality, biography, goals, strengths and preferences.[275]

Each patient should be assessed whereby a care plan is drawn to address issues, such as activities of daily living (ADLs) that can maximise independence, enhance function, adapt and develop skills, and to minimise the need for support.

Assessment and care-planning approach

The following should be assessed:

- Physical health
- Depression
- Possible undetected pain or discomfort
- Side-effects of medication
- Individual biography
- Psychosocial factors
- Physical environmental factors

Behavioural and functional analysis should be undertaken in conjunction with caregivers and care workers.

Individual care plans should be developed and recorded in patients' notes. These should be reviewed regularly with caregivers and other staff.

Adapted from Taylor C *et al*, 2009 [276]

In this section, the intervention is grouped according to the therapeutic goals, with three major domains:

- Maintenance of functions:
  - Adopting strategies to promote independence
  - Maintenance of cognitive functioning.
- Management of challenging behaviours - agitation, aggression and psychosis
- Reduction of co-morbid emotional disorders

6.1 MAINTENANCE OF FUNCTIONS

6.1.1 Strategies for promoting independence

The level of independence for each patient varies and will most likely change with the stage of dementia and the occurrence of other illnesses. It is not uncommon in most Asian cultures that the elderly is refrained from more complex activities, and for others to take over the task for them. There is evidence to suggest that ADL function often deteriorates below what would be expected by the illness alone. So caregivers should encourage the PWD to take a more active role and maintain their independence for as long as possible by creative means and ensuring the right stimulation.[13] Level I, good

There is little research to draw clear conclusions on specific interventions for promoting independence. Despite this conclusion, several strategies are recommended to promote independence. The activities chosen must be individualised according to patient's needs, strengths and limitations.[13] Level III, good

Activities that promotes independence include:

- Communication strategies (e.g. cues, memory books)
- ADL skill training/activity planning
- Assistive technology/telecare/adaptive aids
- Exercise/promoting mobility
- Rehabilitation programmes
- Combination of interventions

NICE[13] Level III, good

a. Communication

Good communication means using simple languages as well as short and concrete sentences to match the level of comprehension. Non-verbal communication will include cues and gestures. Communication can be in the forms of written or pictorial, such as memory book. A memory book consists of individualised images and simple statements that the PWD and caregiver can use to aid the individual's recall and to improve the quality and frequency of communication.

PWD also need to have their vision and hearing tested and corrected with appropriate aids prescribed. For those PWDs who have specific communication problem, speech and language therapist need to be consulted regarding appropriate strategies.[13] Level I, good

b. ADL skill training/Activity planning

Activities of daily living (ADL) skill training can promote independence in personal care tasks (such as bathing, dressing and feeding) and help them to maximise their remaining skills to participate in their own care. Schedule voiding helps in the maintenance of functions. [277] Level I, good

ADL skill training involves assessing people's abilities, their impairments and their task performance in order to understand the underlying physical, psychosocial and neurological issues. The programmes include graded assistance, with the caregiver providing the least amount of assistance needed at each step to complete the task. Strategies may include verbal or visual cues, demonstration, physical guidance, partial physical assistance and problem solving. Professionals trained in assessment and care planning can devise ADL skill training programmes for use by caregivers and/or care staff. [13] Level I, good

c. Assistive technology/Telecare/Adaptive aids

Assistive technology has been defined as any item, product, system or piece of equipment that can be used to maintain, increase or improve the functional capabilities of the person with cognitive, physical or communication disabilities [13] Level III, good

Telecare involves a range of services including virtual visiting, reminder systems, home security, and social alarm systems with the overall aims of avoiding hospitalisation and aiding ageing in place. A telecare package may involve monitoring activity patterns to detect any changes that may warn of potential health changes or of an event such as a fall. Responsive alarms can detect risks by monitoring motion (for example falls) and the presence of fire and gas, and triggering a warning to a response centre or caregiver.[13] Level III, good

Wandering is one of the manifestations of behaviour problems that lead to caregiver distress and early institutionalisation of PWD.[278] It is estimated to occur in 20-25% of community dwelling patients.[279] Electronic tagging and tracking devices such as mobile phone technology and Global Positioning System (GPS) may be viewed as a way of creating a more secure environment for vulnerable PWD who are at risk. [280] Level III, poor;[281] Level III, good However, to date no RCT have been carried out to look into the efficacy of electronic tagging. [282] Level I, good The use of telecommunication system and computer technology may also be used to support distance caregiving, although this has not been fully utilised.[283] Level III, fair

Adaptive aids can range from memory aids to bathing equipment and are aimed at minimising the impact of physical, cognitive and sensory deficits. Similarly, low-level technology (for example lights attached to a movement sensor) is widely used in adaptive aids to minimise risk without the need for action by the user.[13] Level III, good

d. Physical exercise

A combination of structured exercise and conversation can help maintain mobility in PWD, but there is no evidence to support the use of either intervention on its own. The overall impact of physical activities on the symptoms of dementia was minimal. [164] Level I, good)

A Cochrane systematic review based on two RCTs did not find sufficient evidence to suggest that physical activity programmes were beneficial for PWD. A meta-analysis measured by comparison of function at seven weeks to six months (Changes in Advanced Dementia Scale [CADS] and ADL scores) demonstrated that the pooled results were not significant (95% CI -0.1, -0.7 to 0.5).[284] Level I, poor

e. Rehabilitation programme

A systematic review focused on the effects of motor interventions such as physiotherapy, occupational therapy and physical education in PWD found that motor intervention minimised physical and mental decline. [285] Level II-1, poor

The Singapore guidelines underlined structured activity programmes, physical rehabilitation and physical exercise as part of non-pharmacological therapies, but did not elaborate further on these activities. [45] Level III, good

In a RCT (n=165) of mild to moderate patients with dementia, it was found that community based occupational therapy improved daily functioning of the PWD. The NNT were 1.3 at 6 weeks and NNT were 1.5 at 12 weeks. [286] Level I, good

f. Recreational activity

Recreational activities give an opportunity for PWD to engage in meaningful activity, and are often used as a way of facilitating the individual's need for communication, self esteem, sense of identity and productivity. However activities have to be individualised and adapted to maximise the person's remaining abilities. Activities based on previous interests may be more beneficial to PWD than generic activities. [164] Level III, good

g. Combining interventions

PWD do not only experience cognitive impairment, but also physical, emotional and social concerns. Interventions need to target multiple aspects of PWD, the caregivers and environment in order to address the complex needs of the PWD. [13] Level III, good

A qualitative systematic review of 25 studies relating to 22 programmes were analysed according to the caregivers on three outcome measures, that is, mental health, burden and competence. Effects of the programmes on PWD were also looked into and these encompassed mental health, cognitive functioning, behavioural problems, physical functoning, delayed admission and mortality. The conclusion drawn was that the caregiver general mental health was positively affected by combined programmes, while competence appeared promising for women and minority caregivers. For the PWD, combined programmes improved mental health and delayed admission to long stay care. [287] Level I, fair

Recommendation
People with dementia need to engage themselves in meaningful activity. **(Grade C)**
A combination of interventions that promote communication, mobility and cognition is recommended to facilitate independence in these patients. (**Grade B**)
Activities have to be individualised and adapted to maximise the person's remaining abilities. **(Grade A)**
Intervention needs to be integrated to target the person's complex needs, as well as taking into account the caregiver and environmental concerns**. (Grade A)**

6.1.2 Maintenance of cognitive functions

Cognitive functions are the core symptoms of any definition of dementia. The key to improving cognitive functioning is linked to the maintenance of day to day functioning. The evaluation of non-pharmacological interventions in relation to the maintenance of cognitive function is still at an early stage of development.

a. Cognition Oriented Approach

Three major types of approaches with a cognitive focus are:

i. **Cognitive stimulation** entails exposure to and engagement with activities and materials involving some degree of cognitive processing

ii. **Cognitive training** is a specific training exercises geared to specific cognitive functions, and includes practice and repetition which may be computer-assisted

iii. **Cognitive rehabilitation** include working on personal goals, often using external cognitive aids and with some use of learning strategies

NICE[13] Level III,good

A Cochrane systematic review of people with mild to moderate AD or VaD found no evidence for the efficacy of cognitive training.[288] Level I,good Neither was there evidence for cognitive rehabilitation. However, cognitive stimulation produced a modest improvement in cognitive function for patients with mild to moderate dementia. [13] Level I, good

Cognitive stimulation can be given informally through recreational activities, or formally through a programme of memory provoking, problem-solving and conversational fluency activities (reminiscence or reality orientation therapies), spaced retrieval method or face name training. It can be carried out at home by a caregiver, with no risk to the PWD and with minimal training required.[63] Level I, good

b. Reality Orientation Therapy

Reality orientation therapy was developed, based on the belief that continually and repeatedly telling or showing certain reminders to people with mild to moderate memory loss will result in an increase interaction with others and improved orientation. There are two types of Reality Orientation Therapy (ROT): the 24-hours ROT and formal/classroom ROT.

According to SIGN guidelines, ROT may slow cognitive decline and delay nursing home placement. The 24-hours ROT method had more benefits than the formal method. It also suggested that ROT should be administered by a skilled practitioner on an individualised basis.[63] Level I, good A systematic review found a positive effect of the use of Formal ROT on cognition in the domains of information/orientation and memory.[289] Level I, fair

A cross-sectional study (n=50) of probable AD patients found that ROT when combined with integrated sessions of computerised cognitive training, showed beneficial effects on cognitive function, as indicated by an improvement in the mean MMSE scores on admission and at discharge, at 16.0 (SD 5.6) and 17.5 (SD 5.5) respectively, (p=0.005). There was also improvement on ADL and behaviour (mean ADL scores on admission=4.9, mean ADL scores on discharge=5.0). [290] Level III, poor

c. Reminiscence therapy/life review

In reminiscence therapy, past activities, events and experiences are discussed with another person or group of people. It usually involves some tangible prompts such as photographs, household and other familiar items from the past, music and archive sound recordings. Life review on the other hand typically involves individual sessions. The person will be guided through their life experiences, encouraged to evaluate them, and may produce a life story book. Family caregivers are encouraged to be involved in reminiscence therapy.

There was insufficient evidence to evaluate fully the effects of reminiscence therapy in relation to cognitive function in dementia [13] Level I, good;[63] Level I, good

A RCT (n=102) study was carried out for eight weeks duration. Results demonstrated that those receiving reminiscence therapy had significant improvement in cognitive function as measured by MMSE (p=0.015) and affective function by CSDD (p=0.026).[291] Level I, fair

Recommendation

Cognitive stimulation (encompassing both reality orientation and reminiscence therapy) may be offered to improve cognitive function for patients with mild to moderate dementia. **(Grade B)**

6.2 MANAGEMENT OF CHALLENGING BEHAVIOURS- AGITATION, AGGRESSION AND PSYCHOSIS

Behavioural and psychological symptoms of dementia is the result of a complex interaction between the illness, environment, physical health, medication and interactions with others. It is a major source of distress to patients and caregivers, and often significantly impairs quality of life for both. These symptoms often remit spontaneously, but they can also be persistent and severe.

There is lack of evidence to show that pharmacological interventions are effective in the treatment for BPSD. Recent reports had indicated that the use of typical or atypical antipsychotics was associated with increased risk of death [291];[292] Hence it is essential for non pharmacological intervention to be the frontline in the management and treatment of BPSD.

A systematic review showed that caregiver's education, music, physical exercise, recreation, and validation therapy were able to reduce psychological symptoms in PWD. [293] Level I, good

6.2.1 Behavioural management approaches

Behavioural management emerges as one of the stronger non-pharmacological approaches, and appears to have lasting effectiveness for the management of BPSD.

When faced with a patient with challenging behaviours:

- Review possible physical causes
- Examine medication list
- Look for contributing environmental factors
- Consider psychiatric diagnosis
- Focus on target behaviors to be addressed
- Reserve medications for situations where the safety or well being of the patient or others is at risk.

(Adapted from Omelan 2006, Level III, good)

Most of the evidence came from studies targeting co-morbid depression and anxiety in dementia. The evidence in relation to challenging behaviour is less extensive, and largely derives from single case series. There is some evidence that the intervention may need to involve working through others, either family caregivers or paid care workers. It may, inevitably, involve elements of training and support. Consideration should be given to providing access to interventions tailored to the person's preferences, skills and abilities. [13] Level III, good

A systematic review of four RCTS of the behavioural management approach for the treatment of depression in PWD at various stages of dementia severity concluded that there was no evidence for a significant reduction in disruptive behaviour among the nursing home residents or those in the community.[63] Level I, good

6.2.2 Music therapy

Both the NICE guidelines and a Cochrane systematic review based on five RCTs found it difficult to draw any conclusions on the role of music therapy in the care of older PWD. [13] Level I, good ,[294] Level I, good)

In a systematic review of eight small sample size studies, with variations in the application of preferred music interventions (classical music or taped music), compared with no music or other types of treatment conditions (family generated video, social interaction or hand massage), music listening to personal preferences generally had some positive effects on decreasing agitated behaviour in those with dementia. [295] Level I, poor

In a RCT (n=59), the intervention group received 30 music therapy sessions (16 weeks of treatment), and the control group received educational support or entertainment activities. The NPI total score significantly decreased in the intervention group at eight and sixteen weeks (p=0.002). The effect persisted four weeks after end of treatment (p=0.0007), suggesting that subjects allocated to music therapy maintained their improvement over time. Specific BPSD (delusions, agitation, anxiety, apathy, irritability, aberrant motor activity, and night-time disturbances) also significantly improved. [296] Level I, fair

Music therapy stood out as an effective treatment of behavioural symptoms of dementia, especially when tailored to reflect participants' previous tastes. In a systematic review of nursing home residents exposed to a range of musical styles in different settings, music could reduce irritability, fear and depression. When the ratings of irritability, depression and fear were combined, the mean effect size for soothing music was substantial at 0.8 (range 0.7–0.9). The mean effect sizes were 0.3 (range 0.1–0.5) for 1930s jazz and 0.4 (range 0.3–0.5) for pop songs. [293] Level I, good

6.2.3 Physical activity/mobility programme

The SIGN guidelines recommended a combination of structured exercise and conversation to help maintain mobility in PWD. [63] Level I, good 63

A RCT (n=90) which looked into two types of physical activities (gentle comprehensive and walking) and a conversation group, found a higher positive affect as measured by the Observed Affect Scale (OAS) in the gentle comprehensive exercise group (15% in physical activity group > 9% in conversation group, ($p<0.05$). Negative affect scores on the Alzheimers Mood Scale (AMS) were 12% lower in the exercise group than the walking group and 21% lower than the conversation group ($p<0.05$). There were no significant differences for OAS negative affects or AMS positive affects for the physical activity groups noted. [293] Level I, good

A randomised study (n=45) of moderate to severe AD patients assigned either to comprehensive individual exercise, supervised individual walking, or social conversation, demonstrated that 35% of participants had CSDD score < 7, after 16 weeks of treatment. There was also significant changes in the Dementia Mood Assessment Scale score (DMAS) ($p=0.0003$) and the OAS positive affect ($p=0.0092$) after two weeks. The OAS negative affect was not significant ($p=0.1217$). [297] Level I, fair

6.2.4 Validation therapy

Validation therapy is an approach to communicate with disorientated elderly people, which involves acknowledging and supporting their feelings in whatever time and place that is real to them, even if this may not correspond to their "here and now" reality.[63] Level I, good

A systematic review based on four RCTs (n=144), did not find any significant differences between validation and social contact or between validation and usual therapy.[298] Level I, good

The NICE guidelines also concluded that there was insufficient evidence to recommend validation therapy in the treatment of dementia.[13] Level I, good

6.2.5 Multisensory stimulation and/or Snoezelen therapy

The rationale for multi-sensory stimulation and/or Snoezelen therapy, lies in the proposition that the provision of a sensory environment for people with dementia places fewer demands on their intellectual abilities but capitalises on their residual sensorimotor abilities.

There was very little research on Snoezelen therapy or multisensory stimulation in dementia. [13] Level I, good However, two high quality RCTs analysed in a systematic review showed evidence that Multi Sensory Stimulation/ Snoezelen in multi-sensory room reduced apathy in people in the latter phases of dementia. [299] Level I, good

An updated Cochrane systematic review included two new RCTs. There was no effect on behaviour, mood, cognition and communication in either the short or long term follow-up of session based snoezelen programme. Likewise, the 24-hour integrated snoezelen care also failed to demonstrate any effects on the behaviour, mood and interaction in PWD. [300] Level I, good A more recent review concluded that multisensory stimulation proved not effective in treating challenging behaviours in dementia. Some patients are disturbed by its random lights, sounds and shapes. [293] Level I, good

6.2.6 Massage and touch therapy

A Cochrane systematic review based on two small RCTS found evidence to support the efficacy of hand massage for immediate and short-term reduction of agitated behaviour, and the addition of touch and verbal encouragement to eat, for the normalisation of nutritional intake. Massage and touch have been suggested as a non-pharmacological alternative or supplement to other treatments, to reduce or manage anxiety, agitated behaviour and depression associated with dementia. It has also been suggested that massage and touch may counteract cognitive decline.[301] Level I, good

6.2.7 Aromatherapy

Aromatherapy is the use of pure essential oils (such as lavender and melissa) to help relieve health problems and improve the quality of life in general. The healing properties of aroma therapy include promotion of relaxation and sleep, relief of pain, and reduction of depressive symptoms. Aromatherapy has been used to reduce disturbed behaviour, to promote sleep and to stimulate motivational behaviour of PWD.

A RCT on aromatherapy demonstrated a significant effect on measures of agitation, using Cohen-Mansfield Agitation Inventory (CMAI), and NPI, in favour of interventions. However more large scale RCTs are needed to demonstrate the effectiveness of aromatherapy.[302] Level I, good

Both the SIGN guidelines and a recent systematic review did not find any good studies on the role of aromatherapy in reducing the core and associated symptoms of dementia.[63] Level I goodI;[293] Level I, good

6.2.8 Light therapy

Sleep disturbances is common among PWD and give rise to greater risk of mood disorders, poorer daytime functioning, poorer quality of life and increase risk of falls and injuries. It is equally distressing to the caregivers. Available medications proved to be ineffective, with significant adverse effects. Bright light which affects the production of melatonin may be a safer alternative. However three RCTs did not show any consistent benefit of bright light therapy on sleep or agitation.[63] Level I, good

A crossover RCT (n=66) of moderate to severe dementia, exposed to four light conditions (morning bright light, evening bright light, all-day bright light, and minimum standard light) for three weeks, was performed. It was found that night-time sleep increased significantly, with the increase most prominent in severe or very severe dementia (mean increase 16 minutes (p=0.008) for morning, and 14 minutes (p=0.01) for all-day. Effect on daytime sleepiness was however inconsistent. [303] Level I, fair

A RCT (n=189), long term trial (3.5 years), involved patients with dementia exposed to four types of interventions: light, melatonin, combination and placebo. It was found that light has modest benefits on cognition (mean of 0.9 points, 95%CI, 0.0 to 1.7) or 5% improvement on the MMSE and depressive symptoms (1.5 points, 95%CI, 0.2 to 2.7) or 19% improvement on the CSDD. Melatonin has effects on sleep latency (shortened by 8.2 minutes, 95%CI, 1.1 to -15.4) or 19% improvement, and increased sleep duration by 27 minutes (95%CI, 9 to 46) or 6% improvement. Combination therapy reduced aggressive behaviour (3.9 points, 95%CI, 0.9 to 6.9) or 9% improvement on the CMAI, increased sleep efficiency by 3.5% (95%CI, 0.8 to 6.1), and improved nocturnal restlessness by 9% (3.5%, 95%CI, 0.3 to 1.8). Adverse events were dizziness and irritability. [304] Level I, good

Recommendation
Psychosocial interventions should be tailored to individual needs, preferences, skills and abilities of the people with dementia. **(Grade A)**
Specific psychosocial interventions such as music and physical activity programmes can be beneficial in managing behaviour and psychological symptoms of dementia. **(Grade A)**
Multisensory stimulation is not effective in Behaviour and Psychological Symptoms of Dementia, and may be harmful in agitated patients. **(Grade A)**
There is insufficient evidence to recommend massage and aromatherapy. **(Grade A)**
There is insufficient evidence to recommend bright light therapy for sleep disturbances or behavioural and psychological symptoms of dementia. **(Grade A)**

6.3 REDUCTION OF CO-MORBID EMOTIONAL DISORDERS - ANXIETY AND DEPRESSION

Symptoms of depression and anxiety are common in dementia, and are associated with decreased independence and increased risk of nursing home placement. In individuals with dementia, the prevalence of anxiety ranges from 5% to 21% for anxiety disorders, and from 8% to 71% for anxiety symptoms. Cognitive behavioural interventions have been used effectively for many problems (including depression, reduced social skills, acute stress disorder, and problem behaviours) in other cognitively impaired populations. Caregivers may play an important role in the implementation and success of Cognitive behaviour therapy (CBT) in this population.[305]

Cognitive behaviour therapy delivered by trained mental health professionals may be used in the early stages of dementia but is less likely to be effective in the latter stages of dementia or in nursing home setting. However there is a lack of RCT. [13] Level I, good In a systematic review of 19 studies looking into psychosocial intervention, one RCT on behavioural therapy showed limited evidence that, CBT approach using the Behaviour Therapy–Pleasant Events and Behaviour Therapy–Problem Solving, reduced depression in people with probable Alzheimers Disease living at home with their primary caregiver. [299] Level I, good

Bright light therapy had also been looked into as treatment of depression in dementia. In a cross-over RCT (n=66) of patients with moderate to severe dementia exposed to light for duration of three weeks, there was a significant sex differences found in the CSDD scores in response to evening light (p=0.003), all-day light (p=0.001), and standard light (p≤ 0.001). Depressive symptoms were lowest for women and highest for men during morning light. However, findings do not support the use of ambient bright light therapy as a treatment for depressive symptoms in PWD. [306] Level I, fair

A Cochrane review of four RCTs (n=144) on reminiscence therapy showed significant improvement in cognition, mood and functional ability after four to six weeks of treatment among PWD. Participating caregivers of PWD in the reminiscence group also reported lower strain. No harmful effects were reported in the outcome measured. However the review concluded that more robust studies are needed. [275] Level I, good

Recommendation
Cognitive behaviour therapy may be used to treat depression in early dementia. **(Grade B)**
Reminiscence therapy can be used in those with depression and anxiety. **(Grade B)**

7.0 CARE ENVIRONMENT

Environment plays an important role in the development of behaviour problem in dementia. Most people suffering from dementia in this country are still cared for at home by their family members, but institutional care may be inevitable as the disease progresses with changes in the social and family structure.

7.1 ENVIRONMENTAL DESIGNS FOR PEOPLE WITH DEMENTIA

Designs of living environment for PWD and modification of physical environment of their residential areas are largely based on agreed good practice. (Refer to Appendix 12)

There are no RCTs or well designed controlled studies that address the issue of environmental designs, whether in the institution or in the domestic setting, that are appropriate for those with dementia. Most systematic reviews failed to show any benefits, reflecting the lack of high quality research rather than an actual lack of benefit. [307] Level I good ;[282] Level I, good

Environmental modifications, such as, exit modification in the form of subjective barriers has been used to reduce problem behaviours. These include using mirrors, floor stripes and camouflage of door furniture. It may provide an inexpensive, safe, effective and ethical alternative to drugs or restraints in the management of wanderers. However, a Cochrane systematic review found no evidence that subjective barriers prevent wandering. In fact, there is a possibility that such barriers cause psychological harm. [307] Level I, good

The NICE Guidelines based recommendations on four descriptive studies looking into environmental modifications and the use of adaptive aids and other qualitative evidences using interview and observation methods. It looked into the designs of living and care environment for the PWD. Combining adaptive devices with caregiver's education and environmental modifications were reported to improve outcomes in independence for PWD, and at the same time reduced caregivers' stress. When considering environmental design, it was noted that due importance should be given to the differences in individual requirements, which may differ according to the individual's personal history, culture, religion, and the degree of the impairment. [13] Level I, good

The SIGN guidelines [63] Level I, good reviewed the same papers but concluded that changes made to the environment could have a positive impact on the associated symptoms of dementia. However findings of the studies were impaired due to lack of comparison groups, non-equivalent comparison groups and small sample size.

A Cochrane systematic review reported success in terms of adopting a lot of strategies, but outcomes in the area of behavioural difficulties or caregivers' stress and institutionalisation were unknown. [282] Level I, good

The NICE and SIGN guidelines have identified that user involvement in environmental redesign is useful and provides insights. There is currently no evidence on cost effectiveness of environmental redesign related to PWD and their caregiver. [13] Level III, good ;[63]Level III, good

Recommendation

Environmental modification is helpful but needs to be individualised to the person and the degree of impairment, preferably after occupational therapist assessment. **(Grade B)**

The recommended and non-recommended features are listed in Appendix 12

8.0 INTERVENTIONS FOR CAREGIVERS

Caring for a PWD is very challenging, but it can be equally rewarding. The role of the caregiver has been increasingly recognised as the care of the PWD is dependent on them. There is evidence to show an increase in potential costs, both direct and indirect, as a result of psychological distress, physical and mental ill-health, as well as increased mortality among the caregivers. In addition, interventions of caregivers would also benefit the patient, in terms of reducing BPSD, and nursing home placement. Hence the management of dementia should also focus on helping the caregivers. A "one-size-fits-all" approach is deemed ineffective while specific interventions that are tailored towards the needs of the caregiver, implemented at the relevant trajectories of illness, would be most effective.

The Michigan Dementia Coalition-Caregiver Support Workgroup, following a meta-analysis report, made the recommendations for an effective caregiver intervention, as outlined below:

For effective caregiver interventions:

1. **Conduct Assessment-** a thorough assessment of the caregiver and the care giving situation to determine an effective intervention plan that is best suited for the individual circumstance.

2. **Utilise Multi-Component Interventions***- using multiple interventions or techniques simultaneously, increases the chances of effectively addressing the variety of caregiver needs.

   - **Psychoeducation**
     Structured program providing information about the disease process, resources, services and training on how to respond effectively to disease-related behaviours.

   - **Psychotherapy**
     Therapeutic goal to develop problem-solving abilities and help caregiver re-engage in pleasant and positive activities.

   - **Supportive intervention**
     Unstructured support groups to focus on building rapport among participants and creating space to discuss problems, successes, and feelings regarding caregiving.

   - **Respite/day care**
     In-home or site-specific supervision, providing assistance with ADL to give caregiver time off.

   - **Care recipient training**
     Activity therapy programs designed to improve competence of person with dementia.

3. **Offer Interventions with Higher Intensity-** more frequent contacts over a longer period of time are more likely to alleviate caregiver depression and care recipient symptoms.

4. **Promote Consumer-Directed Interventions.** Caregivers who have more choice, control, and flexibility in their home care options are significantly more satisfied with overall service options.

(Modified from Michigan Dementia Coalition-Caregiver Support Workgroup,) [308] Level III

Some of the above Multi-Component Interventions are currently being offered by the Alzheimer Disease Foundation of Malaysia and several patient support groups in Malaysia.

It had been demonstrated that interventions which involve the PWD along side the caregiver appear more effective than interventions that involve the caregiver alone. Among the components of interventions, while psychological therapies had the best outcome on caregiver depression, multi-component interventions had more robust effect on caregiver burden and well-being. [13] level I, good Evidence suggests that caregiver intervention can delay the need for nursing home placement [63] Level I, good

The Resources for Enhancing Alzheimers Caregiver Health study II (REACH II) is a large RCT (n=642) that looked into the effects of a structured and intensive multicomponent interventions (provision of information, didactic instruction, role playing, problem solving, skills training, stress management techniques, and telephone support groups) against usual intervention (educational material and two telephone calls). The primary outcome was a quality-of-life indicator (five domains: caregiver depression, burden, self-care, social support and care recipient problem behaviours) at six months. Differences in net improvement between the groups favoured intervention for both depression (2.6 points net improvement), and problem behaviours (1.5 point net decrease). Secondary outcomes were caregiver clinical depression and institutional placement of the care recipient. The intervention group was found to experience significantly greater improvement in quality of life than those in the control group ($p < 0.001$ [Hispanic], $p=0.0037$ [Caucasian] and $p=0.003$ [African-American]). The prevalence of clinical depression was lower among caregivers in the intervention group (12.6% vs. 22.7%, $p=0.001$), but there were no statistically significant differences in institutionalisation at six months ($p=0.118$).[309] Level I, good

A meta-analysis based on six RCTs on psychosocial interventions (counselling and personal assistance with problem solving), plus offering caregivers a choice of various support strategies and support services, indicated that the odds of institutionalisation (OR=0.60, 95%CI 0.4 to 0.9, $p=0.004$) were less compared to those who received usual care. However time to institutionalisation was not significant (MD=1.6, 95% CI -0.4 to 3.5, $p=0.11$). This study concluded that interventions should be individualized, intensive, and designed to meet the unique needs of patients and their caregivers at the appropriate time.[310] Level I, good

Another RCT comparing counselling and support intervention to usual care had reported a 28.3% reduction in the rate of nursing home placement (HR 0.7, p=0.025) with a difference in median time to placement of 557 days [311] Level II-1, fair

Beneficial effects of caregiver interventions can continue beyond nursing home placement. Burden of the intervention group (comprehensive counselling condition, n=203) was significantly lower than the burden of the usual care group (n=203) at each point after nursing home admission (p<0.03). There was significant reduction of depressive symptoms amongst the caregivers after nursing home admission (p<0.001) and for the accelerated decrease of depressive symptoms after nursing home admission (p=0.009). [312], Level II-1, good

With regards to the duration of effect, caregivers with high morbidity had less total burden and strain 6 months after intervention compared with controls, showing increased burden while at 12 months. All the indices of burden except disappointment were reduced. [313] Level II-1, good

A RCT of PWD-caregiver dyad (n=81) was randomly allocated either to receive the home based intervention (information on dementia, guidance on behaviour management, a single psychiatric assessment and if needed psychotropic medication) or to a waiting list group. The intervention group showed a significant reduction in the outcome measures of General Health Questionnaire (GHQ) (21.1, 95% CI 22.1 to 20.2) and distress due to behavioural disturbances (NPI-D scores) (22.0, 95%CI 23.5 to 20.4). There was a non-significant reduction in the Zarit Burden Score (ZBS), Everyday Abilities Scale for India (EASI) and behavioural problems in the subject (NPI-S) scores. There was also a non-significant reduction in the total number of deaths in people with dementia in the intervention arm (OR=0.3, 95%CI 0.0 to 1.0) observed [314] Level I, good

Recommendation
An evaluation of the caregivers' needs should be carried out on a routine basis. **(Grade A)**
Multi-component* caregiver intervention should be individualised and intensive to meet the needs of patients and their caregivers. **(Grade A)**

*Refer to Michigan Dementia Coalition-Caregiver Support Workgroup

8.1 EDUCATIONAL INTERVENTIONS IN THE MANAGEMENT OF PEOPLE WITH DEMENTIA AND THEIR CAREGIVERS

Information about the disease process, resources, services, and training on how to respond effectively to disease-related behaviours should be provided on a regular basis, preferably as a structured programme. Both the PWD and the caregivers are likely to benefit from enhanced knowledge about the disease, the care giving role, and the available resources. Information is effective as an early intervention strategy to delay more expensive supports. Caregivers may also benefit from training in general problem-solving skills as well as interventions that target behavioural problem or caregivers' emotional response. Psychoeducation along with psychotherapy should be used whenever possible, as research indicates that these two interventions had the most consistent positive effects of caregiver interventions.

There is lack of evidence on educational interventions targeted solely for PWD. Education does appear to be a component of a few other programme including support groups which have had a primary focus on outcomes of depression and anxiety rather than on knowledge and awareness. Most of the research summarised relates to interventions for staff and family caregivers.

Two RCTs and few other descriptive studies that addressed the issue of educational interventions to PWD and their caregiver were reviewed in NICE guidelines[13] Level I, good) and also in the SIGN guidelines[63] Level I, good. It was concluded that PWD and their caregiver are entitled to receive relevant information. A recent narrative review found that psycho-educational or psychotherapeutic approaches have a greater effect than those that use education alone or other type of interventions. Psychoeducation programme had the best outcome in relation to depression apart from psychological therapy (CBT).[315] level III, poor

Recommendation
Educational intervention to both patients and caregivers should be offered. **(Grade C)**

Psychoeducation interventions are listed in Appendix 13

9.0 BASIC LEGAL AND ETHICAL ISSUES

Most patients in the early or mild stage will still have insight into his or her condition. As the disease progress, the mental impairment of dementia brings a gradual loss of understanding, including that of the person's own feelings and behaviour. There will also be a loss of autonomy as patient become more dependent on others. Ethical problems may arise in the context of dementia care as a result of the loss of autonomy and personal freedom.

Underlying the concept of autonomy are two fundamental issues: disclosure of diagnosis and capacity of patient to make decisions.

9.1 Disclosure in dementia or truth telling

Following case identification, the fundamental question is how to disclose the diagnosis of dementia. Most physicians are uncomfortable about disclosure and often would use the patient's relatives and caregivers as a proxy when considering discussion of the diagnosis, treatment and prognosis of the illness, without necessarily having the patient's consent. [316]

Although patients generally would like to know the truth about their own medical condition, the rights of those who do not want to know should also be respected. Health care professionals should therefore seek to understand their patients' preferences with respect to the diagnosis of dementia and act appropriately according to their choice. Studies have shown that the vast majority of patients with mild dementia wished to be fully informed. [45] , Level III, fair

Unless a patient suffering from dementia explicitly declines to know the diagnosis, the default mode should be to inform truthfully as it will enable the patient to:

a. Plan for optimal life experiences in remaining years of intact capacities
b. Designate and appoint a surrogate decision maker to take over the making of treatment decision upon eventual incompetence
c. Settle personal financial and legal matters
d. Participate in treatment decisions
e. Consider possible enrolment in research programmes and
f. Participate in informed consent process

Results from a postal survey of 389 GPs, and 239 neurologists and psychiatrists demonstrated that the two professional groups (70% of the GPs and 77% of the specialists) strongly agreed that "patients with dementia should be informed early because of the possibility to plan their lives". This similar survey also reported in favour of a timely disclosure - an attitude that is more pronounced among younger physicians. [317] Level III, fair

In a cross-sectional study to evaluate relatives' attitudes (n=71) towards informing patients with AD about their diagnosis, 60.6% relatives spontaneously requested that patients not be fully informed, and 54.9% did not want the patient to be told about the lack of disease modifying treatments. Justifications were related to the onset or worsening of depressive symptoms in the patient. A significant degree of denial of AD diagnosis was found in 23.9% relatives. [318] Level III, fair

A small cross sectional study (n=10) of PWD and caregivers highlighted deficiencies in current practice of truth telling and the complexity of the process of disclosing a diagnosis of dementia in an appropriate manner. There is a need to tailor the process of disclosure to individual patients and caregivers. [319] Level III, poor

The Singapore guideline stated the importance of knowing patients preference on the disclosure of the truth, the process of telling, the importance of support after disclosure and reason for disclosure. [45] Level III, fair

Recommendation
Patient's preference on the disclosure of the truth should be elicited. **(Grade C)**
The process of truth telling should be done in an appropriate and sensitive manner. **(Grade C)**
Following disclosure to patient, support should be provided to patients and caregivers. **(Grade C)**

9.2 CAPACITY AND DECISION MAKING

Respect for autonomous decision making is a fundamental ethical and legal right of a mentally competent individual. This right of self-determination should be respected to the fullest possible extent, even in dementia. When affected by dementia, the key to a patient's right of autonomy is the presence of adequate decision-making capacity [45] .

A diagnosis of dementia does not automatically imply a loss of decision making capacity, which is specific to each patient and to each medical decision.[45]

Capacity can be assessed by the patient's ability to:

- Understand the information relevant to the decision.
- To retain this information
- To use or weigh that information as part of the process of making the decision or
- To communicate his decision (whether by talking, using sign language or any other means)

NICE[13] Level III, good

Health and social care professionals should always seek valid consent from PWD. People with dementia should be given the opportunity to convey information in a confidential manner while he or she still has capacity. The PWD and their caregivers should be educated on the use of advance statements (which allow people to state what is to be done if they should subsequently lose the capacity to decide or to communicate) and advance decisions to refuse treatment. [13]

In dementia, the key to a patient's right of autonomy is the presence of adequate decision-making capacity. In Malaysia, once a patient is found to be mentally disordered/incapacitated, the provision of the Malaysian Mental Health Act 2001 (Part X- proceedings in inquires into mental disorder; section 58 to section 75) should be followed, which aims to protect the patient from his or her own harmful decisions or actions.

Recommendation

While the people with dementia still has the capacity, early consideration for advance statements and advance decision to refuse treatment should be planned.(**Grade C**)

When a people with dementia loses decision making capacity, it is important to protect the person from their own harmful decisions or actions. **(Grade C)**

9.3 PALLIATIVE AND END OF LIFE CARE FOR PEOPLE WITH DEMENTIA

The term palliative care encompasses not only the physical symptoms, but also the psychological, social and spiritual aspects of non-curable diseases. The aim is to achieve "the best quality of life for patients and their families" from an early point in the disease [320]. The palliative care approach equate to good-quality person-centred care in dementia. The NICE guidelines advocates specialist palliative care for dementia as that for cancer, particularly towards the end of the patient's life. Both approaches include palliative interventions, which are non-curative treatment aimed at making the patient comfortable, and maximising quality of life, as well as supporting caregivers during their bereavement process. [13] Level I, good

Palliative care in dementia should begin from the time of diagnosis, up to the time of death. Communication about these issues should start as soon as possible, ideally at time when the diagnosis of dementia was made because individuals with dementia eventually lose the ability to make independent decisions about their future care. However, doctors are reluctant to adopt adequate palliative care for people with dementia.

A case control study (n=303) comparing palliative care measures (pain medications and oxygen) in PWD found that only 11% of were given palliative care measures compared to 38% of subjects who were not demented. This finding did not vary significantly with the severity of dementia [321] Level II-3,good

9.3.1 Artificial Nutrition and Hydration

As dementia progresses, the muscles of the throat gradually cease to work properly, leading to swallowing difficulties, gagging, choking, loss of voice, or difficulty catching one's breath. This will compromise nutrition and hydration. People with severe dementia also often lose interest in food and drink. The challenge is whether or not artificial nutrition and hydration should be instituted. However artificial nutrition and hydration is not without problems as findings had shown that it could result burdensome complications such as aspiration pneumonia and pressure sores. Patients often have to be restrained during artificial nutrition and hydration, and this may also prolong survival.

A review of the evidence found no relevant RCTs comparing tube feeding and oral feeding. On the available data, it was concluded that the best evidence did not support the use of tube feeding in dementia. There is a need to weigh the risk and benefit of artificial nutrition and hydration, as it is seldom warranted for patients in the final stages of dementia. Food thickeners with appropriate posture and feeding techniques can be used in patients with dysphagia.[13] Level I, good

A survey of 376 severely demented patients (Global Deterioration Scale Level 7) showed that 24.5% (92) were fed by nasogastric or gastrostomy tube. Despite reservation concerning its utility, feeding tube is reasonably widespread in patients who have reached the stage of severe dementia. [322], Level III, fair

In an observational study of severe dementia (n=178, six weeks duration), a high level of discomfort was found at the time of decision to forgo artificial nutrition and hydration, but the discomfort reduced days thereafter. More than half of the patients (59%) died within one week after the decision was made to forgo artificial nutrition and hydration. Discomfort level were higher in males (1.7 points higher), symptoms of dyspnea and/or restlessness (2.6 and 3.3 points higher, respectively), pain and dehydration (1.5 and 1.3 points higher, respectively) and being awake (3 points higher). [323] Level III, fair)

Recommendation
It is important to individualise and balance the risk-benefit ratio of artificial nutrition and hydration (nasogastric and gastrostomy tube feeding).**(Grade C)**
Alternative conservative measure e.g. posturing, feeding technique and food thickener should be considered. **(Grade C)**

9.3.2 Pain

Pain is a common symptom and there is evidence that pain goes undetected amongst PWD. This reflects difficulties with communication and the recognition of pain by clinicians. There is evidence of under-treatment of pain. [13]

Self-reported pain, although still attainable, may be less reliable in those with mild to moderate dementia than in cognitively intact elderly people, depending on when it is assessed. [324]

The management of pain in dementia should be the same as it is in other branches of medicine. The WHO analgesic ladder is a useful resource (refer to Appendix 13). In the final days of life, a palliative care pathway might encourage appropriate management of symptoms, including pain. [13] Level I, good

An eight week randomised, double-blind, cross-over trial of patients with moderate to severe dementia (n=25) compared acetaminophen (3,000 mg/d) with placebo. Behaviour and emotional well-being were assessed using Dementia Care Mapping and CMAI. As needed psychotropic medication use was aggregated from medication logs. The conclusion was that untreated pain inhibits activity in nursing home residents with moderate to severe dementia. Pain treatment in this group of untreated pain may facilitate engagement with the environment. [325] Level II-1, fair

A three month comparative study (n=163) emphasised the importance of systematic pain assessment in long-term care using Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) in improving pain management practices and decreasing caregiver distress. [326] Level II-3, fair

A quasi-experimental study of older adults (n=126) showed that cognitively impaired participants reported less pain than cognitively intact participants after movement but not at rest. The findings from the study support the use of multidimensional pain assessment in PWD. [324] Level II-3, fair

A systematic review identified 12 observational pain assessment scales for the elderly with severe dementia and evaluated the psychometric properties and clinical utility of these instruments. It concluded (based on the psychometric qualities and criteria regarding sensitivity and clinical utility) that Pain Assessment Scale for Seniors with Severe Dementia (PACSLAC) and DOLOPLUS-2 are the most appropriate scales currently available. [327] Level I, good

Recommendation:
High index of suspicion of the presence of pain and the use of pain assessment scales will be helpful to improve pain detection. **(Grade B)**
Pain in dementia should be treated, the cause of pain determined and managed along WHO analgesic ladder**. (Grade C)** (Refer to Appendix 14)

9.3.3 Treatment of Infection

Pneumonia is common and there is evidence that treatment does not improve mortality and may even cause substantial suffering. However in certain circumstance depending on the severity of the dementia, co-morbidity, immobility, nutritional status and the virility of the infection, antibiotics may be helpful. [13] Level I, good

In a case control study of patients with severe dementia (n=303) against patients without dementia, antemortem data were collected. It was found that 53% of PWD receive antibiotics compared to 41% of those without dementia. It was concluded that use of systemic antibiotics is prevalent in the treatment of patients with late stage dementia, despite the limited utility and discomfort. [321] Level II-3, fair

Recommendation
Antibiotics for treatment of infections and pneumonia in severe and late dementia should be individualised taking into consideration of the severity of dementia, co-morbidity, nutritional status, mobility status and virility of the organism. **(Grade C)**

9.3.4 Restraints

Restraints are used to protect patients with severe dementia from harming themselves because of their behaviour. However the use of restraints can cause some potential problems including risk of harm and injury, further cognitive and functional decline, leading to ultimately loss of independence, as well as loss of confidence and self esteem [45] Level III, poor

A cross sectional study of patients with advanced dementia (n=141), described the last month of life of these patients in long-term care, and the clinical decisions in the management of their end-of-life events. Some form of physical restraint was used on 58.2% (bed-rails and other immobilisers) of patients. Attention to physical suffering was found to be fairly good. However, during the last 48 hours a number of inappropriate interventions were provided. These include tube feeding (20.5%), intravenous hydration (66.6%), antibiotics (71.6%), and life-sustaining drugs (34.0%). [328] Level III, poor

Recommendation
Physical restraint should be used sparingly and individualised. **(Grade C)**

9.3.5 Cardio-Pulmonary Resuscitation

Cardio-Pulmonary Resuscitation (CPR) should not be pursued actively because:

1. The futility and burdensome nature of CPR in severe dementia.
2. The evidence that, in severe dementia, CPR is unlikely to be successful.
3. Evidence from the US show that most older people are against life sustaining treatments. [13] Level I, good

A cross sectional survey of Chinese family caregivers (n=51) on knowledge about CPR, found that family caregivers had poor knowledge about life sustaining treatments, with 59% unable to name any feature of CPR. Most relied on their own views in decision-making rather than on what they thought their relative would have wanted. [329] Level III, poor

Recommendation

Health care professional should have more discussion about Cardio-Pulmonary Resuscitation and make individualised decision after taking consideration of all factors. **(Grade C)**

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Appendix 1

SEARCH STRATEGY

The following free text terms or MeSH term were used either singly or in combination: Alcohol AND dementia; Dementia AND "Down's Syndrome"; "Learning disability" AND dementia; "Intellectual disability" AND dementia; "intellectual disability" and dementia, Dementia AND smoking; depression" AND risk AND dementia; "Early detection" AND dementia; "early recognition" AND dementia; "early diagnosis" AND dementia; (Risk OR "risk factor" OR prevention) AND dementia AND diabetes"; obese OR (Risk OR "risk factor" OR prevention) AND dementia AND obes*"; Risk OR "risk factor" OR prevention} AND dementia AND homocysteine", Risk OR "risk factor" OR prevention) AND dementia AND folate; Risk OR "risk factor" OR prevention) AND dementia AND exercise; (Prevention OR delay) AND dementia AND weight, (Prevention OR delay) AND dementia AND education; "memory clinic" OR "memory clinic attendees"; ("Late dementia" OR "severe dementia" OR "end of life dementia" OR "terminal dementia") AND restraints; (Risk OR "risk factor" OR prevention) AND dementia AND (hypertension OR blood pressure); ("Alzheimers disease" OR Dementia OR Alzheimer) AND "Decision making capacity"; ("Alzheimers disease" OR Dementia OR Alzheimer) AND (Truth OR "truth telling" OR "disclosure); ("Late dementia" OR "severe dementia" OR "end of life dementia" OR "terminal dementia") AND "Artificial nutrition" OR hydration; ("Late dementia" OR "severe dementia" OR "end of life dementia" OR "terminal dementia") AND "treatment of pain"; ("Late dementia" OR "severe dementia" OR "end of life dementia" OR "terminal dementia") AND "treatment of infections"; ("Late dementia" OR "severe dementia" OR "end of life dementia" OR "terminal dementia") AND resuscitation; ("Head injury" OR "brain injury" OR "traumatic brain injury") AND (dementia OR "Alzheimers disease"); ("Mental stimulation" OR "mental activity" OR "mental training") AND dementia; "Social engagement" AND (dementia OR "dementia risk"); Dementia AND "caregivers" OR "caregiver intervention" OR "psychosocial interventions", Screen* dementia, Dementia AND (cognitive screening); Dementia AND "cognitive screening" AND "screening instrument"; "Dementia Screening" AND ("subjective memory complaints" OR "SMC"); ("mild cognitive impairment" OR "MCI") AND (diagnosis OR "assessment); ("mild cognitive impairment" OR "MCI") AND "Montreal Cognitive Assessment"; dementia AND ("assessment of higher order function" OR "assessment of higher executive function"); dementia AND ("verbal

fluency" OR "category fluency"); (dementia" OR "Alzheimers disease" OR AD) AND "measures of progression"; (Dementia" OR "Alzheimers disease" OR AD) AND "severity of dementia"; thyroxine AND dementia; Investigation AND dementia; syphilis AND dementia; VDRL AND dementia; dementia AND ("serum B12" OR "folate" OR "homocysteine); ("diagnostic classification" OR "diagnostic criteria") AND ("Alzheimers disease" OR AD); ("diagnostic classification" OR "diagnostic criteria") AND ("vascular dementia" OR VAD); ("diagnostic classification" OR "diagnostic criteria") AND ("Dementia with Lewy Body" OR "Lewy Body Dementia"); ("Diagnostic classification" OR "diagnostic criteria") AND ("Parkinson's Disease Dementia" OR PDD); ("Diagnostic classification" OR "diagnostic criteria") AND "Frontal Temporal Dementia"; ("Diagnostic classification" OR "diagnostic criteria") AND "Mixed Dementia"; ("Diagnostic classification" OR "diagnostic criteria") AND "Mild Cognitive Impairment"; Dementia AND biomarkers; Biomarkers and DLB; ("Assessment of Depression" OR "Assessment of mood symptoms") AND dementia; ("BehaviouralPsychological Symptoms of dementia" OR "Neuropsychiatric symptoms of dementia") AND "Neuropsychiatric Inventory"; ("Behavior and psychological symptoms of dementia" OR "Neuropsychiatric symptoms of dementia") AND "brief psychiatric rating scale"; ("Behavior and psychological symptoms of dementia" OR "Neuropsychiatric symptoms of dementia") AND "BEHAVE-AD"; (Behavior and psychological symptoms of dementia" OR "Neuropsychiatric symptoms of dementia") AND "Brief Psychiatric rating scales"; "Assessment of functional deficits" AND (dementia OR "Alzheimer disease"); ("Activities of daily Living assessment" OR "ADL assessment") AND (dementia OR "Alzheimer disease"); dementia AND ("Acetylcholinesterase inhibitors" OR Donepezil OR Rivastigmine OR Galantamine); Dementia AND ("Acetylcholinesterase inhibitors" OR Donepezil OR Rivastigmine OR Galantamine) AND (Improvement in cognitive function OR Cognition); Dementia AND ("NMDA antagonist" OR Memantine) AND (Improvement in cognitive function OR Cognition); Dementia AND (Alternative drugs OR Codergocrine mesylate OR Ginkgo biloba OR Nicergoline OR Nimodipine OR Hyergine OR NSAIDS OR Estrogen OR Fish Oils OR Vitamin E OR Vitamin B12 OR Lecithin OR Folate OR Sage) AND Improvement in cognitive function OR Cognition OR Memory OR Language OR Orientation OR Concentration OR "Executive function" OR Learning); "Fatty Acids, Omega-3"[Mesh] AND "Dementia"[Mesh]; dementia AND "Ginkgo biloba"[Mesh];"Lecithins"[Mesh] AND "dementia"; dementia AND "Ergoloid Mesylates"[Mesh]; dementia AND "Salvia officinalis"[Mesh]; "Dementia"[Mesh] AND "Vitamin E"[Mesh]; "Dementia"[Mesh] AND "Anti-Inflammatory Agents, Non-Steroidal"[Mesh]; Dementia/drug therapy [MeSH] AND Non-cognitive; Dementia AND Drug therapy AND Non-cognitive; Dementia OR AD OR Alzheimers OR Alzheimers

Disease OR Mild cognitive impairment AND Pharmacotherapy OR Drug therapy; Dementia [MeSH] AND Antipsychotics AND "Non-cognitive", Dementia [MeSH] AND Antipsychotics AND "Non-cognitive"; Dementia AND Antipsychotics AND [BPSD OR behavioural OR neuropsychiatric]; Dementia [MeSH] AND Anxiolytics Dementia [MeSH] AND Hypnotics; Dementia [MeSH] AND Antidepressants; Dementia [MeSH] AND "Acetylcholinesterase inhibitors" OR "Memantine", Dementia [MeSH] AND Antimanic OR "Mood stabilisers" Dementia [MeSH] AND Selegiline; Dementia [MeSH] AND Lithium, "Dementia" AND "combination therapy"; Dementia AND "Dual Therapy"; Dementia AND "Combination treatment"; Dementia AND "Augmentation Therapy"; Dementia AND Pharmacological AND "Non-Pharmacological therapy"; Dementia AND "Drug and psychosocial interventions"; Dementia AND "Combination treatment"; (Dementia OR "Alzheimers disease" OR Alzheimers OR AD) AND ("strategies for promoting independence" OR "psychosocial intervention" OR "behaviour intervention" OR "non pharmacological intervention"); (Dementia OR "Alzheimers disease" OR Alzheimers OR AD) AND ("Activities of daily living training" OR "cognitive rehabilitation" OR "cognitive training" OR "cognitive stimulation activities" OR psychological intervention" OR "physical activity program" OR "reminiscence therapy" OR "reality orientation" OR "validation" OR "setting suitable for dementia" OR "social engagement"); (Dementia OR "Alzheimers disease" OR Alzheimers OR "BPSD" OR "Behavioural and psychological symptoms of dementia" OR "neuropsychiatric symptoms of dementia") AND ("Aroma therapy" OR "Multisensory stimulation" OR "Snoezelen therapy" OR "Group psychotherapy" OR "social engagement" OR "Music therapy" OR "Physical activity program" OR "massage and touch therapy" OR "reminiscence therapy" OR "reality orientation" OR Validation therapy" OR "behaviour therapy" OR "animal assisted therapy" OR "white noise"); (Dementia OR "Alzheimers disease" OR Alzheimers) AND (Depression OR "Anxiety) AND ("Psychological intervention" OR "non pharmacological intervention" OR "cognitive rehabilitation" OR "cognitive training OR "cognitive stimulation activities" OR "physical activity" OR "reminiscence therapy" OR "reality orientation" OR "validation therapy" OR "social engagement" OR "art therapy" OR "music therapy" OR ECT OR electroconvulsive); (Dementia OR "Alzheimers disease" OR Alzheimers OR AD) AND (Environment OR "Environmental design" OR "suitable setting" OR "subjective barriers" OR "therapeutic garden" OR "design of dining areas" OR "bright light therapy"); ("Dementia caregivers" OR "Alzheimers Disease caregivers" OR "Alzheimers carers" OR "AD caregivers") AND (psychoeducation OR "educational interventions" OR "supportive intervention" OR psychotherapy OR "training of care recipient" OR "multi-component intervention" OR "staff training");

Appendix 2

CLINICAL QUESTIONS

1. What are the groups of people who are at increased risk of developing dementia?
2. For people at risk of developing dementia, are there any non-pharmacological strategies to prevent or delay the onset of dementia?
3. Are there advantages/disadvantages to early identification of dementia?
4. Is a person with dementia capable of making decisions?
5. Is truth-telling beneficial for patients with dementia?
6. Are these interventions (artificial feeding and hydration, pain treatment, infection treatment, restraints, resuscitation) beneficial for patients with late/severe dementia?
7. Are these interventions beneficial for patients with late/severe dementia?
8. What are the roles of memory clinic?
9. Are assessments of needs helpful to dementia caregivers?
10. Are interventions for caregivers beneficial?
11. Is routine cognitive screening for those 60 years and above at the primary care level useful to detect early dementia?
12. What are the tools suitable for screening people at risk of dementia at the primary care level?
13. When should patients with dementia be referred to a tertiary specialist service?
14. What are the brief cognitive tests that can help in the diagnosis of mild cognitive impairment or early dementia or dementia, at the secondary/tertiary care level?
15. How can one determine the progression of dementia?
16. What relevant investigations are needed to rule out treatable causes of dementia?
    - ❑ Routine blood investigation
    - ❑ Thyroid function tests
    - ❑ Tests for syphilis
    - ❑ Serum B1, B12
    - ❑ Serum folate and Homocysteine level

17. Are there diagnostic classifications of dementia for different subtypes of dementia?
    - ❑ ICD10
    - ❑ DSM-IV
    - ❑ NINDS- AIREN, ADDTC or HACHINSKI ISCHEMIC SCORE or Rosen
    - ❑ Modified Score
    - ❑ Lund- Manchester Criteria
    - ❑ MCI criteria
18. Are biomarkers useful in the diagnosis of dementia (AD, VAD, FTD, DLB/PDD)?
19. How should non-cognitive functions be assessed?
20. How do you determine the functional difficulties in patients with dementia
21. What is the role of CT and MRI brain in patient with dementia ?
22. What is the role of PET /SPECT in the diagnosis of dementia?
23. What is the role of EEG's in the diagnosis of Dementia?
24. For people with dementia do acetyl cholinesterase inhibitors/NMDA antagonist when compared to placebo cause improvement in cognitive function?
25. What are the other choices of drugs (other than acethylcholinesterase inhibitors/ memantine that produce benefit or harm compared with an appropriate comparator?
26. For people with vascular dementia do drugs (anti-dementia drugs and drugs that control vascular risk factors) when compared to placebo cause improvement or decline in cognitive function?
27. For people with dementia do drug treatment when compared to placebo cause improvement in non- cognitive function?
28. In healthy adults, is there any pharmaceutical product in the prevention of dementia?
29. In patient with dementia, are there any combination treatments for cognitive and non- cognitive symptoms of dementia which produce benefit or harm?
30. For patients with dementia are the strategies for promoting independence produce benefits/harm in the specified outcome?

31. For people with dementia does cognitive rehabilitation produce benefit or harm?
32. Do psychosocial/behavioural interventions (aromatherapy, reality orientation, validation therapy, reminiscence) for management of behaviour/psychological symptoms (BPSD) of dementia patient produce benefit or harm?
33. For people with dementia what environmental designs are appropriate compared to standard care?
34. Are educational interventions useful in the management of people with dementia and their caregivers?

Appendix 3

MALAY- MINI MENTAL STATE EXAMINATION

Introduction

Three versions of the Malay-MMSE (M-MMSE) have been validated in a group of Malay-speaking elderly population in Malaysia [116] Scores lower than the optimal cut-off scores indicate cognitive impairment. Please refer to the table below for the appropriate cut-off scores for each of the three versions of the M-MMSE based on the education level and gender.

- ❏ M-MMSE-7 refers to serial 7s
- ❏ M-MMSE-3 refers to serial 3s instead of serial 7s
- ❏ M-MMSE-S refers to asking the patient to spell the word 'dunia' backwards instead of serial 7

Table 9. The optimal cut-off scores for the screening of dementia forM-MMSE-7, M-MMSE -3, M-MMSE-S.

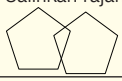
	M MMSE-7	M MMSE-3	M MMSE-S
Combined male and female	≤21	≤18	≤17
Male	≤23	≤22	≤19
Female	≤19	≤18	≤18

Malay MMSE Assessment Type: .....

Patient ID: ..... Date:.....

Sex: Male ☐ Female ☐

Educational level: Primary ☐ Secondary ☐ Tertiary ☐

Maximum	Markah pesakit	
5		*Orientasi Masa*
		Tahun, bulan, hari, tarikh, waktu (+/- 1 jam)
5		*Orientasi Tempat*
		Negara, Negeri, Bandar,Tempat (hospital/rumah), bilik (wad/klinik)
3		*Pendaftaran*
		Saya akan menguji ingatan awak. Sila dengar dengan teliti, tiga objek yang saya akan baca, iaitu, oren, kunci dan sikat. Sila sebut semula tiga objek tadi. Ingat betul-betul, kerana saya akan bertanya kemudian.
5		*Perhatian dan Pengiraan (sila guna salah satu kaedah)*
		M-MMSE-7: Sila tolak 7 dari 100 dan teruskan. *M-MMSE -3*: Atau, tolak 3 dari 20 dan teruskan. *M-MMSE-S*: Atau, ejakan perkataan 'DUNIA' dari belakang ke depan.
3		*Ingat Kembali*
		Sila sebut kembali 3 objek yang telah disebut tadi.
2		*Penamaan*
		Namakan benda ini. (Pensel dan Jam Tangan)
1		*Ulangan*
		Sebutkan 'Tidak mungkin dan cukup mustahil'
3		*Arahan tiga peringkat*
		Ambil kertas dengan tangan kanan, lipat setengah dan letakkan atas lantai/meja.
1		*Pembacaan*
		Baca dan lakukan …..TUTUP MATA ANDA
1		*Penulisan*
		Tulis satu ayat yang lengkap.
1		Penyalinan
		Salinkan rajah berikut 
Jumlah		

Appendix 4

THE ICD-10 CLASSIFICATION OF MENTAL AND BEHAVIOURAL DISORDERS

DEMENTIA

G1. Evidence of each of the following:

(1) A decline in memory, most evident in the learning of new information.

- Mild: A degree of memory loss sufficient to interfere with everyday activities, but still compatible with independent living.
- Moderate: A degree of memory loss causing a serious handicap to independent living. Only highly learned material is retained.
- Severe: Only fragments of previously learned information remain. The subject fails to recognize even close relatives.

(2) A decline in other cognitive abilities characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information.

- Mild: Individual is independent but complicated daily tasks or recreational activities cannot be undertaken.
- Moderate: The individual is unable to function without the assistance of another in daily living.
- Severe: The decline is characterized by an absence, or virtual absence, of intelligible ideation.

G2. Preserved awareness of the environment

Absence of clouding of consciousness. When there are superimposed episodes of delirium the diagnosis of dementia should be deferred.

G3. A decline in emotional control or motivation, or a change in social behaviour, Manifests as at least one of the following: (1) emotional lability; (2) irritability; (3) apathy; (4) coarsening of social behaviour.

G4. For a confident clinical diagnosis:

G1 should have been present for at least six months.

Comments: The diagnosis is further supported by evidence of damage to other higher cortical functions, such as aphasia, agnosia, apraxia. Judgment about independent living or the development of dependence (upon others) needs to take account of the cultural expectation and context.

F00 DEMENTIA IN Alzheimers Disease (for details please refer to ICD 10)

A. The criterias G1 to G4 must be met.

B. There is no evidence from the history, physical examination or special investigations for any other possible cause of dementia.

Comments: The diagnosis is confirmed by post mortem evidence.

Specification of features for possible subtypes:

Because of the possibility that subtypes exist, it is recommended that the following characteristics be ascertained as a basis for a further classification: age at onset; rate of progression; the configuration of the clinical features, particularly the relative prominence (or lack) of temporal, parietal or frontal lobe signs; any neuropathological or neurochemical abnormalities, and their pattern.

Subdivision of dementia in Alzheimers disease:

F00.0
Dementia in Alzheimers Disease with early onset

F00.1
Dementia in Alzheimers Disease with late onset

F00.2
Dementia in Alzheimers disease, atypical or mixed type

F00.9
Dementia in Alzheimers disease, unspecified

Appendix 5

DSM-IV CLINICAL CRITERIA FOR DIAGNOSIS OF DEMENTIA

Cognitive domain	Questions
Amnesia	Any forgetfulness? Did it start gradually or suddenly? Is it progressively worse? And if so, is it smoothly declining or showing a step-wise/fluctuating decline? Is it over short-term or long-term matters?
AND declines in one of the following domains:	
Aphasia	Any word-finding difficulty or other difficulties with communication?
Apraxia	Any problems with buttoning or dressing? Any difficulties with using utensils during meal times?
Agnosia	Any problems recognising familiar faces or familiar items?
Executive dysfunctioning	Any problems handling money (loose change)? Any change in general problem solving abilities? Is one's work becoming more disorganised?
OF sufficient severity to cause significant impairment in social or occupational functioning	As a result of the above, is the patient becoming less independent in the - community? - home-care? - self-care level?

(Source: American Psychiatric Association [165]. Diagnostic and Statistical Manual of Mental Disorders, 1994 & Singapore MOH Clinical Practice Guidelines 3/2007)[45],[180]

Appendix 6

290.00 DIAGNOSTIC CRITERIA FOR DEMENTIA OF THE Alzheimers TYPE (based on DSM- IV TR)

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 recognize or identify objects despite intact sensory function)

(d) disturbance in executive functioning (ie, planning, organizing, 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 characterized 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 (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)

(2) systemic conditions that are known to cause dementia (eg, hypothyroidism, vitamin B12 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 (eg, Major Depressive Disorder, Schizophrenia).

Code based on type of onset and predominant features:

With Early Onset: if delirium is superimposed on the dementia

290.11 With Delirium: if delirium is superimposed on the dementia

290.12 With Delusions: if delusions are the predominant feature

290.13 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature.

290.10 Uncomplicated: if none of the above predominated in the current clinical presentation. With Late Onset: if onset is after age 65 years.

290.3 With Delirium: if delirium is superimposed on the dementia

290.20 With Delusions: if delusions are the predominant feature

290.21 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature.

290.00 Uncomplicated: if none of the above predominates in the current clinical presentation

Specify if: With Behavioural Disturbance

Coding note: Also code 331.0 Alzheimers Disease on Axis III
(Source: SIGN [63] Guideline 2006)

Appendix 7

DISCLOSURE OF PROGNOSES AND DIAGNOSES

Good practice in the disclosure of prognoses and diagnoses

Giving 'bad news'

- Use patient-led communication
- Tailor your approach for each individual
- Remember that this is a dynamic and ongoing process
- Identify any potential benefits of knowing the diagnosis
- Instill hope

Diagnosis disclosure-suggested guidelines

- Use a multi-professional approach to answer questions and make recommendations
- Consider telling patient and caregiver together
- Allow each separate time to talk and ask questions
- Arrange follow-up meetings to continue discussions
- Discuss how the disease might progress
- Agree to a care plan
- Provide written educational materials
- Provide a list of community resources and contacts
- Arrange for further support e.g. supportive individual or group counselling

Adapted from Pinner & Bouman (2003). [330]

Table 10 : ACETYLCHOLINESTERASE INHIBITORS [270]

Drugs	Donepezil	Rivastigmine	Galantamine
Dosage	5 mg od at bedtime, increased after one month to 10 mg od Max: 10 mg od	Oral route: 1.5 mg bd, increased to 3 mg BD by minimum of 2 weeks according to response and tolerance; Max: 6 mg bd Transdermal/patch: Initial dose is 4.6 mg once daily and increased to the 9.5 mg once daily, after a minimum of 4 weeks according to response and tolerability.	Initially 4 mg bd. Increased to 8 mg bd after 4 weeks. Maintenance 8-12 mg bd
Dosage in renal failure	No dose adjustment	No dose adjustment	In moderate renal impairment, reduced dose ≤ 16 mg/day. In severe renal impairment (creatinine clearance < 9 ml/min), galantamine is NOT recommended
Dosage in hepatic insufficiency	No dose adjustment	No dose adjustment	Moderate hepatic impairment (Child-Pugh score of 7 to 9), total daily dose ≤ 16 mg/day In severe hepatic impairment (Child-Pugh score of 10 to 15), it is NOT recommended.
Common adverse events	Gastrointestinal: Diarrhea, loss of appetite, nausea, vomiting Musculoskeletal: Cramp Neurologic: Insomnia Others: Fatigue	**Capsule** Gastrointestinal: Nausea, vomiting, diarrhea, loss of appetite, abdominal pain Metabolic: Weight loss Neurologic: Dizziness, headache **Transdermal patch** Gastrointestinal: Diarrhea, nausea, vomiting	Gastrointestinal: Nausea, vomiting, diarrhea, loss of appetite Endocrine metabolic: Weight loss Neurologic: Dizziness, headache
Precautions	Anesthesia with succinylcholine • Asthma or obstructive pulmonary disease • Cardiac conduction abnormalities (SVT, AV block) • Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) • Gastrointestinal disease or history of ulcer disease • Seizure history	• Anesthesia withsuccinylcholine • Asthma or obstructive pulmonary disease • Extrapyramidal symptom, increased incidence or intensity of tremor • Seizure history; • Peptic ulcers or gastrointestinal bleeding; • Urinary obstruction • Sick sinus syndrome or other cardiac conduction conditions.	• Anesthesia with succinylcholine • Asthma or obstructive pulmonary disease • Cardiac conduction abnormalities (SVT, AV block) • Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) • Gastrointestinal disease or history of ulcer disease • Seizure history

TABLE 11: N-METYL-ASPARTATE RECEPTOR ANTAGONIST (MEMANTINE)

Drug	Memantine
Dosage	Initial dose: 5 mg OD. The dose should be increased in 5 mg increments to 10 milligrams/day (mg/day) given as 5 mg bd, 15 mg/day given in separate doses of 5 mg and 10 mg, and 20 mg/day given as 10 mg bd. The minimum recommended interval between dose increases is 1 week The recommended maintenance dose is 10 mg bd
Dosage in renal failure	If creatinine clearance (CrCl), <30ml/min: dose adjusted to 5 mg bd If creatinine clearance >30 ml/min: No dose adjustment required
Dosage in Hepatic insufficiency	No information
Common adverse effects (Commons)	**Cardiovascular** : Hypertension **Gastrointestinal** : Constipation **Neurologic** : Dizziness, Headache, Pain
Precautions	• Concomitant use of drugs that make the urine alkaline, the clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8 (eg: Sodium Bicarbonate, Carbonic anhydrase inhibitors (eg: Acetazolamide, methazolamide)) • concomitant use of other NMDA antagonists • genitourinary conditions that raise urine pH; may increase plasma levels of memantine • moderate to severe renal impairment. • seizure disorder

Table 12 : ANTIPSYCHOTICS

Drug	Starting dose	Maximum dose	Adverse effects
Risperidone	0.5 mg daily	2 mg daily	Rash, hyperprolactinemia, weight gain, abdominal pain, constipation, diarrhea, increased appetite, indigestion, nausea & vomiting, Extrapyramidal syndrome, including Parkinsonism, excessive salivation and akathisia, dizziness, headache, insomnia, somnolence.
Olanzapine	2.5 mg	10 mg	Chest pain, orthostatic hypotension, peripheral edema, tachyarrhythmia, hyperlipidemia, xerostomia hyperglycemia, increased appetite & weight gain, constipation, indigestion, Extrapyramidal disease, Parkinsonian abnormal gait, akathisia, asthenia, dizziness, somnolence.
Quetiapine	12.5 to 50 mg daily	200 to 300 mg daily	Orthostatic hypotension, tachycardia hyperlipidemia, xerostomia, weight gain, constipation, increased appetite increased liver enzymes, asthenia, dizziness, extrapyramidal disease, headache, insomnia, sedated, somnolence, agitation, fatigue.
Aripripazole	5 mg daily	15 mg daily	Weight gain, constipation, nausea & vomiting, akathisia, dizziness, extrapyramidal disease, headache, insomnia, sedated, somnolence, tremor, anxiety, restlessness, fatigue.
Black box warning	• Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death; most deaths were attributed to cardiovascular events (e.g. heart failure or sudden death) or infections (e.g. pneumonia) • Cerebrovascular adverse events (stroke, transient ischemic attack) including fatalities, have been reported in elderly patients with dementia-related psychosis.		

(Source: MICROMEDEX ® HEALTHCARE SERIES, Vol 141 Version 2009 [270])

Table 13 : ANTIDEPRESSANTS

Name	Starting	Maximum	Renal failure	Hepatic insufficiency	Adverse Effects
Selective Serotonin Reuptake Inhibitors					
Sertraline	25 mg	150 mg	No adjustment	Lower or less frequent dose	Weight gain, bloating, constipation, xerostomia, asthenia, dizziness, headache, somnolence, nervousness, blurred vision, urinary retention, rash, sweating, abnormal ejaculation, reduced libido, orgasm incapacity, fatigue
Fluoxetine	20 mg	40 mg	No adjustment	Lower or less frequent dose	
Escitalopram	10 mg	20 mg	Caution in severe RF	No adjustment	
Fluvoxamine	25 mg	300 mg	No adjustment	Lower start dose and monitor dose increase	
Precautions: • Increased risk of developing cardiac abnormalities • Cardiovascular disease - cardiac conduction defects, arrhythmias, congestive heart failure, myocardial infarction, stroke, tachycardia • Hyponatremia					
Serotonin and Noradrenaline Reuptake Inhibitor (SNRIs)					
Venlafaxine	37.5 mg	225 mg	Dose adjustment	Lower or less frequent dose	Nausea, insomnia, dry mouth, somnolence, dizziness, sweating, nervousness, headache, sexual dysfunction. Hypertension.
Noradrenergic and specific Serotonergic Antidepressants (NaSSA)					
Mirtazepine	15 mg	30 mg	Caution in renal failure	Monitor dose increase	Increased appetite, weight gain, drowsiness, oedema, dizziness, headache, blood dyscrasia. Nausea/sexual dysfunction uncommon

(Source: MICROMEDEX ® HEALTHCARE SERIES, Vol 141 Version 2009 [270])

Appendix 12

ENVIRONMENTAL DESIGNS APPROPRIATE FOR PEOPLE WITH DEMENTIA

General Recommendations

A) Institution

Unit size:

- Give consideration to the size of units, mix of residents and the skill mix of staff to ensure that the environment is supportive and therapeutic.
- Smaller units are associated with gains that include less anxiety and depression, greater mobility, increase in supervision and interaction between caregiver and residents, higher motor functioning, improve or maintenance of ADL's and lowers level of strain and better attitude to dementia care.

Dining:

- Food not served in tray and served in a common dining room.

(Modified from NICE guidelines)[13] Level III,good

Other recommendations:

- Simulated home environment/show rooms in the hospital/community settings.
- Usual care consists of education materials and booklet describing home environment safety tips.
- Safety devices (alarms, child proof locks) - No study reports outcome of using this electronic devices [282]
- Floor with coarse-textured coverings, shining, with sharp colour contrast and highly patterned surfaces can be misinterpreted as change in level by people with impaired depth perception.[13]

Special recommended features

B) Domestic setting

- When organising living arrangements and/or care homes for PWD, must ensure that built environment are enabling and aid orientation. Attention should be given to lighting, colour schemes, floor coverings, assistive technology, signage, garden design and the access to and safety of the external environment.
- Incorporate outdoor areas with therapeutic design features.
- Using covers over fire exit bars and door knobs helps to reduce unwanted exiting.
- Tactile way finding cues, good lighting and windows allowing daylight to enter, view of external landmarks may help PWD to find their way around the indoor environment.
- Colors may also used to assist with orientation.
- Highly visible toilets may potentially reduce level of incontinence.
- Providing moderate level of environmental stimulation is also recommended such as murals on walls.
- Wandering paths are recommended.

(Modified from Singapore guidelines) [45]

Appendix 13

EDUCATIONAL INTERVENTIONS IN THE MANAGEMENT OF PEOPLE WITH DEMENTIA AND THEIR CAREGIVERS:

Recommendations

1. Both PWD and their caregiver are entitled to receive relevant information regarding dementia, treatment, available support services, as well as legal, financial and benefits advice.

This can be done through: Written information

- Individual or group psychoeducatio
- Counselling
- Telemedicine services
- Training courses about dementia, services and benefits, communication and problem solving in the care of people with dementia
- Cognitive Behaviour Therapy
- Stress management
- Peer support groups tailored to the needs of individuals depending on the stage of dementia by telephone and through internet
- Involvement of other family members as well as the primary caregiver in family meetings

2. Components of psychoeducation:

- Disease information, diagnosis, investigations and treatment
- Medication used -efficacy and side effects
- Strategies to improve independence
- Medico-legal issues including driving and finance
- Communication skills
- Stress management
- Grief work

(Modified from NICE[13] and SIGN[63])

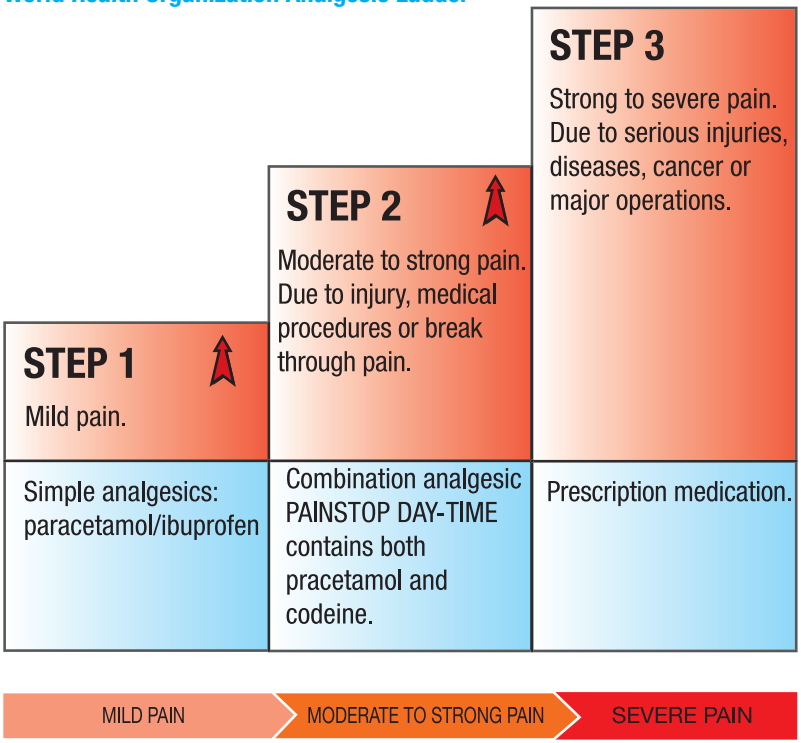
Appendix 14

WHO PAIN LADDER

WHO three-step "ladder"

If pain occurs, there should be prompt oral administration of drugs in the following order: nonopioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. To calm fears and anxiety, additional drugs -"adjuvants" -hould be used. To maintain freedom from pain, drugs should be given "by the clock", that is every 3-6 hours, rather than "on demand" This three-step approach of administering the right drug in the right dose at the right time is inexpensive and 80-90% effective. Surgical intervention on appropriate nerves may provide further pain relief if drugs are not wholly effective.

World Health Organization Analgesic Ladder



Source: http://www. Painstop.com.au/gallery/images/underst.

ABBREVIATIONS

AChEI	Acetylcholinesterase inhibitors
AD	Alzheimer disease
ADAS-Cog	Alzheimer Disease Assessment Scale- Cognitive
ADL	Activities of daily living
ADAS-Cog	Alzheimer disease Assessment Scale-Cognition
ADCS-ADL	Alzheimers Disease Cooperative Study–Activities of Daily Living
AUC	Area Under The Curve
AβPP	amyloid β-protein precursor
BADL	Basic activities of daily living
BEHAVE-AD	Behavioural Pathology in AD Rating Scale
BPRS	Brief Psychiatric Rating Scales
BPSD	Behavioural and psychological symptoms of dementia
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy
CBT	Cognitive Behaviour Therapy
CDR	Clinical Dementia Rating
CDR-SB/CDR-SOB	Sum Boxes of Clinical Dementia Rating Scale
CPR	Cardio-Pulmonary Resuscitation
CGIC	Clinical Global Impression of Change
CGI scale	Clinical Global Impression scale
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CJD	Creutzfeldt-Jakob disease
CI	Confidence Interval
CMAI	Cohen Mansfield Agitation Inventory
CNS	Central Nervous System
CSF	Cerebrospinal fluid
CSDD	Cornell Scale for Depression in Dementia
CT	Computed tomography
CVFT	Categorical Verbal Fluency Test
DAD	Disability Assessment for Dementia
DLB	Dementia with Lewy bodies
DSM-IV-TR	Diagnostic statistical manual, 4th edition, revised version
ECAQ	Elderly Cognitive Assessment Questionnaire
EEG	Electroencephalography
FBI	Frontal Battery instrument
FTLD	Frontotemporal lobar degeneration
FTD	Frontotemporal dementia
GDS	Geriatric Depression Scale
HR	Hazard ratio

IADL	Instrumental Activities Of Daily Living
ICD-10	International Classification Diagnostic manual, version 10
ITT-LOCF	Intention to treat - last observation carried forward
IQCODE	Questionnaire on Cognitive Decline in the Elderly
LR	likelihood ratio
LOCF	Last Observation Carried Forward
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MADRS	Montgomery-Asberg Depression Rating Scale
MoCA	Montreal Cognitive Assessment
NPV	negative predictive value
NMDA	N-methyl-D-aspartate
NNH	Number Needed To Harm
NNT	Number Needed To Treat
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
NPs	Neuritic plaques
NSAIDs	Non-steroidal anti-inflammatory drugs
OAS	Observed Affect Scale
OC	Observation carried forward
OMR	Overall Misclassification Rate
OR	Odds Ratio
PET	Positron Emission Tomography
PDD	Parkinson Disease Dementia
PIB	Pittsburgh Compound B
PPV	Positive predictive value
PWD	People with dementia
RCT	Randomised Controlled Trial
ROT	Reality Orientation Therapy
RR	Relative risk
SD	Semantic Dementia
SIB	Severe Impairment Battery
SPECT	Single Photon Emission Controlled Tomography
SDS	Symptoms of Dementia Screener
SMC	Subjective Memory Complaint
SSRI	Selective Serotonin Reuptake Inhibitor
Sn	Sensitivity
Sp	Specificity
TCAs	Tricycyclic antidepressants
VaD	Vascular Dementia
WMS	Weschler Memory Scale

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