Practical Manual of Dementia in Older Adults



Third Edition

Brain Health Special Interest Group

The Hong Kong Geriatrics Society
香港老人科醫學會

PREFACE

The long awaited third edition of this “dementia booklet” as called by most colleagues, finally was born. It has been already 8 years in 2014 when the second edition was produced. In this new edition, the Brain Health Special Interest Group (SIG) has collectively decided on several major changes. The first is that apart from a hard copy, there will be in parallel, an electronic mobile version on web. Secondly this soft version is designed to be revised anytime in any part of it whenever the Brain Health SIG judges that it is necessary. The timeliness of revision can then be achieved without reverting to the revision of the whole manual in a hard copy format. Therefore, this third edition is probably the last hard copy edition. Please treasure it when one reaches you. Thirdly, the mobile version has been inserted with hyperlinks to the references and can “jump” to the specific part of the manual when the content is referring to that part. It can help the efficiency of reading and cross referencing.

The manual section sequence has also been revised so that it can follow an ordered approach in the diagnosis and management of dementia. Section 1 now is “First Time Assessment and Clinical Diagnostic Approach of Different Presentations in Neurocognitive Disorders”. This serves as a guiding schema for clinicians during initial evaluation of a patient presented with neurocognitive problem. It can then be examined if the provisional diagnosis fulfills any of established diagnostic criteria (Section 2), though it is not mandatory in clinical practice, unlike that for research purpose. The severity or staging of the disease can be made reference to Section 3 by different assessment scales so that an appropriate plan can be formulated accordingly. After diagnosis and staging, appropriate investigations (Section 4, Neuroimaging and AD Biomarkers) can then be carried out to identify and ascertain the “clinicobiological” diagnosis of the neurocognitive disorder. After the diagnosis is made, management (Section 5), no matter non-pharmacological or pharmacological, and future care plan in late stage (Section 6) should then be explored and discussed. We hope the revision of the section sequence can augment the practicability of a clinical approach.

Finally, the term “dementia” has continued to be in the mainstream in geriatric medicine since our last edition, in contrast to neurocognitive disorders, and therefore this new addition has followed the first edition and renamed as “Practical Manual of Dementia in Older Adults”.

Last but not least, I would like to take this opportunity to thank the Editorial Group Members and all Members in Brain Health SIG for giving invaluable opinions and comments in this edition. In addition, I would like to thank several colleagues outside The Hong Kong Geriatrics Society, Mr. CHIU Chung Yee, Charles, Ex-Chairman of the Guardianship Board, Dr. YEUNG Tsz Wai, Kayla, Neuro-radiologist of Tuen Mun Hospital, Dr. CHO Wan Chi, Valda, Clinical Psychologist of Caritas Medical Centre, and the Occupational Therapy Teams of Castle Peak Hospital and Kwai Chung Hospital and the Physiotherapy Team of United Christian Hospital. I feel indebted to all of them because without their expertise, this edition can never be materialized.

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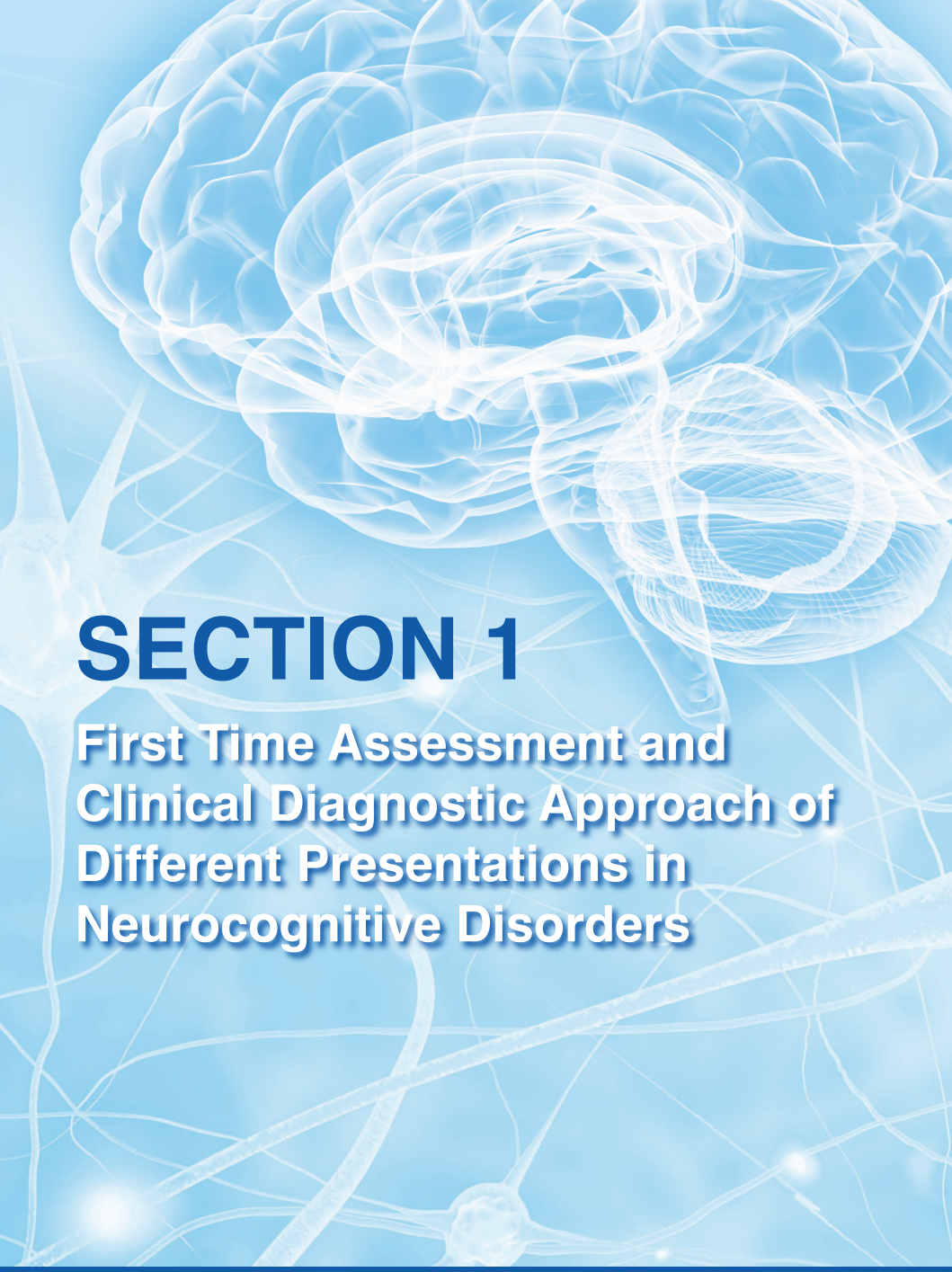

SECTION 1

First Time Assessment and Clinical Diagnostic Approach of Different Presentations in Neurocognitive Disorders

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First Time Assessment and Clinical Diagnostic Approach of Different Presentations in Neurocognitive Disorders

1.1 First Time Assessment of Neurocognitive Disorders

1.1.1 Practical Guide for First Time Assessment

This guide is by no means exhaustive and can be shortened and lengthened depending on the clinical context. Do not use it as a prototype questionnaire. Clinical assessment is an art and the flow of communication among the clinician, patient and caregiver can often change and shift during the consultation. Most likely, all of the followings cannot be done in one session because it will be too long and the patient will become tired. Modify it according to your own work setting.

History (collect history from informant – family member, caregiver or close friend)

- Age and sex
- Past or current occupation (retirement year)
- Years of education
- Smoking and alcohol habit

Chief Complaint

Cognitive Deficits (suggested questions)

- Initial/prominent symptoms (memory vs. non-memory domains) and onset/duration/progression (slow vs. rapid onset/progression)
- Memory problem: recent episodic memory loss (misplaced objects, repeat questions or conversations, forget recent events: e.g. forget to turn off stove? forget appointments? forget to pay bills or to take medications? forget meals?)
- Attention (e.g. easily distracted? periods of decreased alertness?)
- Disorientation: time, place, person.
- Perceptual problems (e.g. get lost in neighborhood? cannot recognize family members? fail to see something right in front of them?)
- Executive function (e.g. lose the ability to use a mobile phone or operate an electrical appliance?)
- Language difficulty (naming, fluency and comprehension of speech and communication)
- Social cognition (e.g. behave appropriately in social situations? impulsive, careless or unguarded?)

SECTION 1

First Time Assessment and Clinical Diagnostic Approach of Different Presentations in Neurocognitive Disorders

Behavioral and Psychological Symptoms of Dementia (BPSD) (common examples)

- Mood: depression, anxiety, apathy, euphoria, irritability
- Psychotic: delusion, hallucination (delusion of theft by domestic maid, visual hallucination of seeing miniature people and deceased relatives)
- Behavioral: withdrawal, agitation/aggression, disinhibition, impulsiveness, inappropriateness, motor disturbance (wandering in the street, sleep and nighttime behavior disturbance)
- Vegetative: sleep disturbance (altered sleep wake cycle, sun-downing, rapid eye movement (REM) sleep behavior disorder); appetite/eating disorder (hyperorality, anorexia)

Motor Symptoms

- Falls, walking difficulty

Functional Assessment (Impairment in Activities of Daily Living (ADL))

- Basic ADL: selection of appropriate clothes, continence status
- Instrumental ADL: telephone, finance (banking, paying bills), shopping, cooking, medication management, travelling alone
- Social activities and hobbies: lost interest in past hobbies (e.g. playing Mahjong, watching TV, reading newspaper)

Systems Review

- Past health: diabetes mellitus, hypertension, hyperlipidemia, stroke, atrial fibrillation (AF), obstructive sleep apnea (physical and psychiatric comorbidities and other geriatric syndromes/sensory impairment)
- Drug history: anti-cholinergic drugs, sedatives
- Family history: neurocognitive disorder
- Social history: living situation, caregiver (knowledge/coping strategy/stress), social/community support
- Sexual history: HIV, syphilis

Physical Examination

- General impression: apathetic/agitated/sociable
- Cardiovascular: irregularly irregular pulse (AF), bruits, heart murmur
- Focal neurological sign, muscle tone, muscle power, tendon reflexes
- Parkinsonian sign, downward gaze palsy
- Frontal release signs
- Gait

Do not omit other systemic examination (you could miss a paraneoplastic syndrome presenting as dementia).

Neuropsychological Tests

Depending on the setting and time constraint and resources, find an appropriate set of tests you find practical and you are familiar with. Note the affect and attention during the test.

Suggested list:

- Abbreviated Mental Test (AMT)
- Mini-Mental State Examination (MMSE)
- Montreal Cognitive Assessment (MoCA)
- Clock Drawing Test (CDT)
- Clinical Dementia Rating (CDR) Scale
- Motor sequencing test – slap/fist/cut

Please refer to Section 1.1.4: Neuropsychological Tests at First Time Assessment and Section 3: Assessment Scales in Neurocognitive Disorders for details.

Investigations

Laboratory Tests

- Complete blood picture, renal and liver function
- Blood glucose, lipid profile
- Thyroid function
- Serum vitamin B12 and folate levels
- Syphilis serology (optional), HIV Ab (if suspicious)

ECG

- Note AF (vascular dementia), long QT interval (neuroleptic treatment precaution), bradycardia

Neuroimaging

- Structural imaging (for potentially treatable causes e.g. brain tumor, hydrocephalus, subdural hematoma; assess cortical/hippocampal atrophy, vascular contributions): plain CT brain is basic, MRI brain is a preferred modality

Other Potentially Useful Tests:

- Functional imaging (FDG PET (18F-fluorodeoxyglucose positron emission tomography), SPECT (single-photon emission computed tomography))
- Pathological imaging (amyloid PET)
- CSF examination for biomarkers (amyloid beta (Aβ), tau for Alzheimer's disease (AD); protein 14-3-3 and RT-QuIC for Creutzfeldt–Jakob disease (CJD))
- EEG (esp. for CJD)
- Genetic testing

Please refer to Section 4: Investigation – Neuroimaging and AD Biomarkers for details.

Diagnosis

- Type and stage (use Functional Assessment Staging Test (FAST) scale if AD suspected)

Please refer to Section 1.1.3: Pattern Recognition in Different Subtypes of Major Neurocognitive Disorders for details.

Management

Social aspects

- Prognosis information
- Financial arrangement
- Advance care planning (ACP)
- Enduring power of attorney (EPA)
- Caregiver stress/community services/respite care/daycare resources

Please refer to Section 6: Late Stage Dementia for details.

Medical aspects

- Vascular risk factors control
- Non-pharmacological treatment (do not ignore this)
- Pharmacological treatment (it may not be the most useful part)
- Follow-up

Please refer to Section 5: Management for details.

1.1.2 Clinical Staging of Neurocognitive Disorders

The following algorithm can be used in assessing a patient with cognitive problem:

History Taking from/Concern of a Patient or a Knowledgeable Informant [1.1a] [1.1b] [1.1c] [1.1d] [1.1e] [1.1f]
Objective Cognitive Assessment/from Longitudinal Cognitive Testing

↓

Assess Different Cognitive Domains: [1.1a] [1.1b] [1.1c] [1.1d]

1. Memory and learning
2. Complex attention
3. Executive function
4. Language
5. Perceptual-motor
6. Social cognition

↓

Assess Function (at work or usual/everyday activities) [1.1a] [1.1b] [1.1c] [1.1d]

↓

Exclude Other Causes (e.g. delirium, mental disorders, medical/neurological diseases, medication/substance use) [1.1a] [1.1b] [1.1c] [1.1d]

MNEMONIC of Reversible Causes of Neurocognitive Disorders [1.1e]

- **D**rugs: anti-cholinergic, anti-psychotic, hypotension
- **E**motional: depression
- **M**etabolic: vitamin B12 deficiency, hypothyroidism, diabetes mellitus
- **E**ars and visual deficits
- **N**ormal-pressure hydrocephalus
- **T**umors and other space-occupying lesions
- **I**nfection: sinus infections, HIV, syphilis
- **A**trial fibrillation
- **S**leep apnea

After using the above algorithm, cognitive problem can be classified as follows:

	Normal Cognition [1.1a]	Transitional Cognitive Decline (TCD) / Subjective Cognitive Decline (SCD) / Mild Behavioral Impairment (MBI) [1.1a][1.1b]	Mild Cognitive Impairment (MCI) / Mild Neurocognitive Disorder [1.1a][1.1b][1.1d][1.1f][1.1g]	Dementia / Major Neurocognitive Disorder [1.1a][1.1b][1.1c][1.1d]
Subjective complaint	No recent cognitive decline or new neurobehavioral symptoms reported by self or observer	A subjective report of cognitive decline which is a concern of the individual	Modest cognitive decline from a previous level of performance (both subjective concern and objective assessment) [1-1.5SD (7-16th percentile) below average for NIA-AA 2011 criteria or >1.5SD below average (<7th percentile) for Petersen's criteria or 1-2SD below average (3rd-16th percentile) for DSM-5 criteria]	Significant cognitive decline from a previous level of performance (both subjective concern and objective assessment) [<2SD below average (<2nd percentile) for DSM-5 criteria]
Objective assessment	Normal performance within expected range on objective cognitive tests No recent decline from longitudinal cognitive testing	Normal performance within expected range on objective cognitive tests ± subtle decline on longitudinal cognitive testing		
Cognitive domains involved		Cognition is a core feature. Mild neurobehavioral changes may co-exist (termed mild behavioral impairment)	Amnestic Non-amnestic Single domain Multiple domains	Significant decline in ≥2 cognitive domains (in NIA-AA 2011 criteria) vs. ≥1 cognitive domain (in DSM-5 criteria)
Occupational and social functioning	Normal function	Normal function	Essentially independent function but possibly with increasing difficulty in complex activities	Interfere with independence in daily activities
Conversion rate	1-2% per year for older adults (≥65 years) [1.1h]	6.6% per year to MCI 2.3% per year to dementia [1.1i]	5-15% per year to dementia [1.1j]	

Please refer to Section 2.1: Dementia/Major Neurocognitive Disorder (Major NCD), Section 2.2: Mild Cognitive Impairment (MCI)/Mild Neurocognitive Disorder (Mild NCD) and Section 2.2.5: Practical Notes on Pre-MCI Stage: Transitional Cognitive Decline (TCD), Subjective Cognitive Decline (SCD), Mild Behavioral Impairment (MBI) for details.

1.1.3 Pattern Recognition in Different Subtypes of Major Neurocognitive Disorders

Major neurocognitive disorders can be further classified into different subtypes by pattern recognition clinically as follows:

Dementia Subtypes	Main Clinical Features
Alzheimer's disease (AD)	Slow onset and gradual progression, episodic memory impairment
Vascular dementia (VaD)	Stepwise deterioration, temporal relation with stroke, physical signs consistent with stroke
Dementia with Lewy bodies (DLB)	Parkinsonism (within 1 year of cognitive symptom onset), recurrent vivid visual hallucination, fluctuating cognition, REM sleep behavior disorder, severe autonomic dysfunction, neuroleptic sensitivity
Parkinson's disease dementia (PDD)	Cognitive symptoms after at least 1 year of parkinsonism motor features (1-year rule), some shared features with DLB but less prominent, executive dysfunction most prominent
Behavioral variant of frontotemporal dementia (bvFTD)	Behavioral disinhibition, apathy or inertia, loss of sympathy or empathy, stereotyped or compulsive/ritualistic behavior, hyperorality or dietary changes, executive dysfunction Please refer to Section 2.5.4: Practical Notes on FTD
Primary progressive aphasia (PPA)	Language difficulty Non-fluent variant: agrammatism, speech apraxia Semantic variant: impaired object naming, impaired single-word comprehension, impaired object knowledge, surface dyslexia or dysgraphia Logopenic variant: impaired single-word retrieval in spontaneous speech and naming, impaired repetition of sentences and phrases, speech (phonologic) errors in spontaneous speech and naming
Progressive supranuclear palsy (PSP)	Cognitive dysfunction with impaired vertical gaze, early presentation of falls, postural instability and akinesia
Normal pressure hydrocephalus (NPH)	Development of apraxic gait → then urinary incontinence (urge) → dementia
Alcohol-related dementia	Heavy drinker, amnesia and frontal lobe features ± cerebellar signs and chronic liver disease signs
Creutzfeldt-Jakob disease (CJD)	Rapidly progressive dementia (over weeks or months), pyramidal/extrapyramidal symptoms, visual or cerebellar disturbance, myoclonus or akinetic mutism
HIV infection, neurosyphilis	Sexual history

1.1.4 Neuropsychological Tests at First Time Assessment

Neuropsychological assessment is a method of examining the brain by studying its behavioral product.[1.1k] [1.1l] It can assist in diagnosing the dementia subtype, its severity and progression by detecting the pattern of cognitive deficits. It can also help testing the capacities involving vocational and self-care and also normal adult rights and privileges (e.g. driving licence, right to give medical consent or legal competency). However, the latter needs comprehensive neuropsychological evaluation which is beyond the scope of first time assessment.

Mental state examination is often performed as the first part of the neuropsychological assessment because it informs us the reliability of the remainder of the testing. It usually covers the followings:

1. Level of alertness/arousal: e.g. alert, drowsy, stuporous, comatose. Impairment on this level would limit the usefulness of comprehensive test of higher level processing.
2. Comment on affect: general behavior and insight during the examination/ interview. This assessment is important because depression and dementia share some similar behavioral presentations. Depression can cause over-report of the severity of cognitive disturbance while depression and dementia can co-exist.
3. Orientation: time, place, person, purpose
4. Other tests commonly used at bedside to assess higher level processing (language, motor, visuoperceptual and visuospatial skills, memory, executive functioning and comportment): e.g. Serial 7s, registration and memory of three objects at five minutes, digit span (forward and backward), name the chief executive, clock drawing, name five cities, following simple commands (e.g. 1-step, 2-step). For more standardized testing or for testing of higher cortical functions, cognitive screenings (e.g. MMSE and HK-MoCA) could be considered.

These tests can be supplemented by more detailed or comprehensive neuropsychological evaluation by clinical psychologists trained in neurocognitive disorders if deemed necessary.

SECTION 1

First Time Assessment and Clinical Diagnostic Approach of Different Presentations in Neurocognitive Disorders

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1.2 Clinical Diagnostic Approach of Different Presentations in Neurocognitive Disorders

1.2.1 Amnesia in Neurocognitive Disorders

Amnesia is a deficit in memory caused by brain damage or disease or use of certain medications. Memory is the mental function which enables us to acquire, retain and recall sensations, impressions, information and thoughts we have experienced. Most people think of memory as either short-term or long-term. However, memory can be divided into many more types (as shown in Figure 1).

There are three memory stages: sensory, short-term and long-term. Information processing begins in sensory memory, moves to short-term/working memory, and finally moves into long-term memory.

There are two main types of long-term memory: explicit (conscious or declarative) and implicit (unconscious or non-declarative) memory. Explicit memory are those experiences and information that you have to consciously think about to remember. It consists of information which is consciously stored and retrieved and requires conscious recall. Implicit memory refers to knowledge you remember unconsciously and effortlessly.

Explicit memory can be divided into episodic and semantic. Episodic memory is the ability to remember (recent and distant) episodes of your life. Semantic memory stores your knowledge of facts, concepts, names and other general knowledge information about the world.

Implicit memory can be divided into procedural memory, classical conditioning, priming and non-associative learning. Procedural memory is implicit memory for skills and motor movements. It involves those skills and tasks you learn and perform without conscious awareness. Classical conditioning refers to the unconscious awareness of an association of one stimulus with another stimulus. Priming is an effect in which exposure to one stimulus influences the response to another stimulus due to prior experience. Non-associative learning (habituation or sensitization) is when you are not pairing a stimulus with a behavior (repeated exposure to a stimulus decreases one's responsiveness to the stimulus).

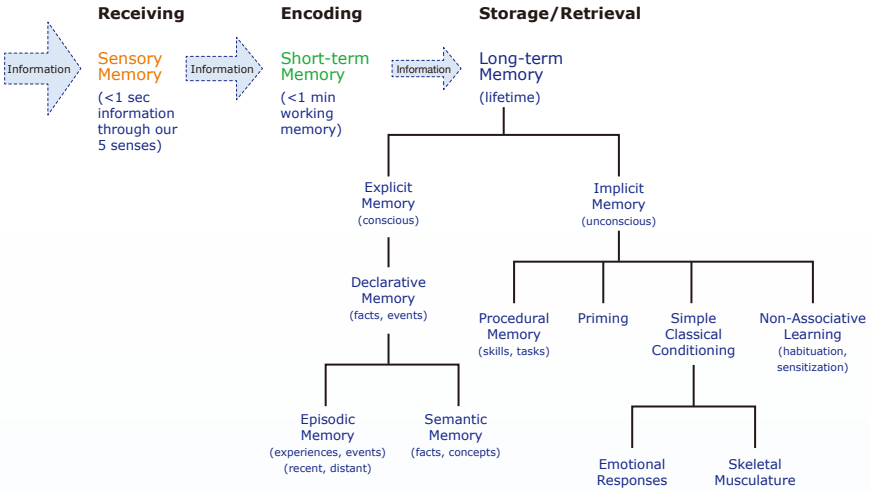

Figure 1. Classification of different types of human memory.[1.2.1a]

Clinical Approach

In patients presented with memory problem (amnesia), it is important to assess the type(s) of memory deficit as follows:

1. Episodic memory deficit (hippocampus and surrounding structures in the temporal lobe are important in episodic memory and are part of default mode network, which includes several brain areas including frontal and parietal lobes)
   - Forget recent events? cannot acquire and remember new information?
     Like semantic memory, remote memory eventually becomes independent of the hippocampus and appears to be "stored" more broadly in the neocortex. Likely because of this unique neuroanatomy, remote episodic memories do not tend to be as severely disrupted as recent episodic memories in neurodegenerative diseases (e.g. AD)
   - Free recall or cued recall or with recognition?
     Amnestic syndrome of hippocampal type is a recall deficit that does not significantly improve with cueing or recognition procedures. Normative data from cross-sectional studies examining neuropsychological performance demonstrate that the ability to perform new learning or acquisition declines with age, whereas cued recall remains stable.[1.2.1b]
   - Suggested questions: e.g. forget to turn off stoves? forget appointments? forget to pay bills or to take medications? forget meals?
   - Screening test: 5-items delayed recall in HK-MoCA with category cues and multiple-choice cues
   - Specific test: Free and Cued Selective Reminding Test

2. Semantic memory deficit
   - Forget facts or general knowledge?
   - Suggested questions e.g. forget what a car is and how an engine works?
   - Screening test: ask the name of government leader in AMT
3. Procedural memory deficit
   - Forget skills or procedure?
   - Suggested questions e.g. forget how to use a cooker for a housewife? tying shoelaces or swimming?
   - Screening tests: name as many words that begin with letter “F” in 1 minute, state the letters of the alphabet, alternating with sequential numbers (i.e. “A1B2” and so on)
   - Specific tests: pursuit rotor task (follow a moving object with a cursor), serial reaction time task, mirror tracing task
4. Working memory deficit (working memory is more closely related to attention and falls under the domain of executive function, which involves the frontal cortex and parietal lobe)
   - Ask about tasks that require someone to focus
   - Suggested question e.g. need more time handling coins at the supermarket?
   - Screening tests: digit span (forward and backward) test, Serial 7s, state months of the year in reverse order

Each type of memory uses a different network in the brain. Therefore, one type can be affected by any disease or injury while another type functions normally. The type(s) of memory deficit can provide diagnostic clues to the dementia subtypes as follows:

Memory Deficit	**Dementia Subtypes Commonly Affected** (not exhaustive)
Episodic memory deficit	AD
Semantic memory deficit	Semantic variant PPA
Procedural memory deficit	PDD
Working memory deficit	VaD, Lewy body disease (LBD), bvFTD

We should evaluate the involvement of other cognitive domains, motor symptoms and neurological signs, behavioral and neuropsychiatric symptoms, and comorbid medical conditions. Significant positive findings guide us to the appropriate potential diagnosis. Please refer to Section 1.1.3: Pattern Recognition in Different Subtypes of Major Neurocognitive Disorders for details. Further laboratory and radiological investigation should follow the protocol of global cognitive impairments. Please refer to Section 4: Investigation – Neuroimaging and AD Biomarkers for details.

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1.2.2 Executive Dysfunction in Neurocognitive Disorders

In the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), executive function is one of the cognitive domains affected by neurocognitive disorders. However, the DSM-5 does not recognize executive function disorder as a specific mental health condition. Instead, executive function issues are symptomatic of other neurological, mental health, and behavioral disorders. [1.2.2a]

Executive function refers to a set of cognitive abilities that enable adaptive, goal-oriented behavior. These include the ability to think flexibly, inhibit what is irrelevant, plan, and adjust behavior as appropriate. It encompasses 6 aspects that can be differentially affected in individual patients.

1. Planning
2. Decision making
3. Working memory (ability to temporarily process and manipulate information in conscious awareness. Patients with working memory deficits find it challenging to focus.)
4. Feedback/error utilization (ability to benefit from feedback to infer the rules for solving a problem)
5. Inhibition (ability to hold back a predominant, automatic response that may be inappropriate or irrelevant in the present context. Patients with cognitive inhibition deficit may appear easily distracted, stimulus bound, and impulsive.)
6. Mental/cognitive flexibility (ability to shift between two concepts, tasks, or response rules, to modify attention and behavior in response to changing circumstances and demands.)

Individuals with executive dysfunction require increased effort to complete multistage projects, have increased difficulty multitasking or difficulty resuming an interrupted task. They may report that large social gatherings are more taxing or less enjoyable because of increased effort required to follow shifting conversations. In moderate and severe stage, they may abandon complex tasks and rely on others to plan instrumental activities of daily living or make decisions.

Executive function relies on distributed neural networks involving the prefrontal cortex, parietal cortex, basal ganglia, thalamus, and cerebellum. Therefore, any neurologic process that involves these regions may cause executive dysfunction, and the list of differential diagnosis of executive dysfunction is also extensive.[1.2.2b]

Clinical Approach

Executive dysfunction is observed in patients with VaD, LBD, bvFTD, early-onset AD, and other neurodegenerative conditions. The clinical evaluation of patients should follow the assessment of global cognitive impairment, with a comprehensive history and neurologic examination. Since patients sometimes only report their memory loss and fail to tell their functional impairment, we should ask specific questions, including difficulty with planning or organization, problems with multitasking, poor judgment or decisions, impaired concentration/short attention span, difficulty with problem-solving, mental rigidity/inflexibility, and impulsivity.

Some screening tests for global cognitive impairment, such as HK-MoCA, are sensitive for detecting executive dysfunction. Other neuropsychological tests are designed to assess individual executive function domains.

Planning	Interpret a sequential picture or object arrangement
Decision making	Simulated gaming, scenario and problem solving
Working memory	Digit span (forward and backward) test, Serial 7s, dot counting tasks
Inhibition	Stroop Color-Word Interference Test
Mental/cognitive flexibility	Trail Making Test, Wisconsin Card Sorting Test

We should evaluate the involvement of other cognitive domains, motor symptoms and neurological signs, behavioral and neuropsychiatric symptoms, and comorbid medical conditions. Significant positive findings guide us to the appropriate potential diagnosis.

Emotional, behavioral symptoms	bvFTD
Gait problem, neuromotor symptoms	PDD, Parkinson plus syndrome, VaD
Visual hallucination	LBD
History of cerebrovascular and cardiovascular disease	VaD

Cognitive inhibition deficit is different from disinhibited behavior, which suggests distinct anatomy and differential diagnosis. The clinical diagnosis of bvFTD is based on the core behavioral criteria of an insidious and progressive personality change with impairments in social interpersonal conduct, impairments in regulation of personal conduct, early emotional blunting, and early loss of insight.[1.2.2c] Behavioral symptoms, include disinhibition, apathy and sociopathy, are common in early stage, but they are not the inhibition deficit in executive dysfunction. At later stage of disease, dorsolateral prefrontal regions are involved, executive function such as cognitive flexibility declines.

Further laboratory and radiological investigation should follow the protocol of global cognitive impairments.

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1.2.3 Speech and Language Problem in Neurocognitive Disorders

Language is the ability to encode ideas into words or symbols for communication; it involves speaking, comprehending, reading, and writing. Speech is the motor aspect of spoken language production; it encompasses articulation and the production of vocal sounds.

The left hemisphere of the brain is particularly connected with speech and language functions. There are two specific areas of the brain. Broca's area in the posterior frontal lobe (influent speech) and the Wernicke's area in the temporal lobe (fluent speech but lack of content), lesions over there give rise to typical patterns of language impairment (aphasia).

Speech and language disorder is common in different types of dementia. It affects the communication between patients and their caregivers and subsequently patients' quality of life. The most common speech impairments connected with dementia include apraxia of speech and dysarthria. People with apraxia of speech have trouble pronouncing sounds. They speak slowly with impaired rhythm and inconsistent errors. Dysarthria is caused by impaired movement of the muscles related to speech. It is manifested by mumbled speech, small and monotonous voice, articulation error. Language impairments involve expression, comprehension, or both. People with language impairments may use irrelevant words (paraphasia), make grammatical mistakes (agrammatism), misunderstand words, fail to name objects (anomia), or repeat sentences. Those symptoms are not unique for one type of dementia, but language impairments in the early stages are the characteristics of AD and PPA. [1.2.3a]

Alzheimer's Disease

In the early stages of AD, patients show mild word-finding difficulties with occasional semantic substitutions (saying aunt instead of sister), but their speech remains fluent and grammatically correct. This is known as anomic aphasia. With progression, anomia worsens, and comprehension is affected. In the moderate to severe stages, their speech becomes influent and less in amount. In the severe stages, patients exhibit echolalia (follow and repeat words or phrases said by someone) and verbal stereotypies (repeat meaningless words or phrases).

Primary Progressive Aphasia

PPA is a clinical syndrome characterized by gradual onset, isolated language impairment in the early stages. Episodic memory and other cognitive domains are primarily unaffected until the later stages, and language function is the most impaired domain throughout the disease.

Based on the language impairment pattern, there are variants of PPA: non-fluent/agrammatic, semantic/fluent, and logopenic. Non-fluent and semantic variants are included as the clinical frontotemporal dementia syndromes, while the logopenic variant is associated with Alzheimer's pathology.

	Alzheimer's Disease		Primary Progressive Aphasia		
	Early-stage	**Late-stage**	**Non-fluent**	**Semantic**	**Logopenic**
Spontaneous speech	Fluent, grammatical	Non-fluent, echolalia	Apraxia of speech, short, word finding difficulty	Fluent, grammatical, word finding difficulty	Slow, grammatical, word finding difficulty
Paraphasia	Semantic	Semantic & phonemic	Phonemic	Semantic	Semantic
Repetition	Intact	Impaired	Impaired	Intact	Impaired
Naming	Intact ±	Impaired	Impaired	Impaired	Intact
Comprehension of words	Intact	Impaired	Intact	Impaired	Intact
Reading	Intact	Impaired	Impaired	Impaired	Impaired
Writing	Intact	Impaired	Impaired	Impaired	Impaired
Word & object knowledge	Intact ±	Impaired	Intact	Impaired	Intact
Associated dementing syndromes			Behavioral symptoms of motor neuron disease, corticobasal degeneration (CBD)	Behavioral symptoms of FTD	AD

Table 1. Summary of language impairments in Alzheimer's dementia and primary progressive aphasia.[1,2,3b]

Clinical Approach

The assessment for language deficit symptoms should be started with comprehensive history taking, same as for global cognitive impairment. Corroborating history from caregivers about changes in the spoken language production, comprehension, reading, and writing should be collected. We should especially enquire for the examples of speech-related "memory loss", which may indicate difficulties of word-finding and misinterpretation of word meaning instead of memory problems.

Listening to a patient's spontaneous speech can be done by asking open-ended questions, which is an essential part of language assessment. We should pay attention to articulation, fluency (rate of speech, phrase length), grammatical accuracy, and word-finding (pause for word search and vocabulary range).

Naming is another crucial aspect of language assessment, the types of errors can be informative. We can ask the patient to describe a complex picture or the consultation room. Phonemic (substitution of one sound with another) or semantic (substitution of a word related to the target) errors can differentiate non-fluent or fluent progressive aphasia. Circumlocution describes what a word means instead of providing the name, and visual agnosia is a failure to recognize what an object is. They are observed in both early AD and other semantic dementia. Other components of language function can also be evaluated by various assessment methods (Table 2).

Language Domain	Assessment Methods
Naming	• Ask the patient to name items around the room or on your person • Ask the patient to name the pictures on the 15-item CERAD naming

Repetition of sentences	• Ask the patient to repeat unfamiliar sentences/phrases, e.g.
	  • No ifs, and, or buts
	  • Go into the garden and pick up the beans
	  • The judge sentenced the criminal
	  • The prime minister lives in Ottawa

Comprehension (auditory)	• Ask the patient to perform
	  • Single one-step commands
	  • Followed by two-step commands
	  • Followed by three-step commands
	• Can give grammatically complex commands

Comprehension (semantic knowledge)	• Ask the patient to define words or perform tasks requiring decoding of semantic knowledge, e.g.
	  • Point to a source of illumination
	  • Point to the surface that you walk on
	  • Define island, pyramid

Reading	• Ask the patient to read the following commands and perform them:
	  • Close your eyes
	  • Touch your nose
	  • Before touching your chin, point to the ceiling
	  • Open your mouth after you point to your chair and the floor
	• Ask the patient to read a paragraph from the newspaper or magazine—observe for reading effort, pronunciation of words, melody

Writing	• Ask the patient to write a sentence to examine for grammar, spelling errors, phrase length, and punctuation, e.g.
	  • Why the patient came to see you
	  • A description of the weather or a picture shown to them
	• Ask the patient to write a sentence to dictation
	• Ask the patient to copy a sentence

Table 2. Formal language assessment. [1.2.3b]

Further laboratory and radiological investigation should follow the protocol of global cognitive impairments.

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1.2.4 Behavioral and Psychological Symptoms in Neurocognitive Disorders

Behavioral and psychological symptoms of dementia are defined as signs and symptoms of disturbed perception, thought content, mood and behavior which are similar to those seen in psychiatric disorders. Clinically it can be classified into cognitive/perceptual (e.g. delusions and hallucinations), motor (e.g. pacing, wandering, repetitive movements and physical aggression), verbal (e.g. calling out, repetitive speech, yelling and verbal aggression), emotional (e.g. euphoria, depression, apathy, anxiety and irritability), and vegetative (disturbances in sleep and appetite).

Virtually all patients with dementia will develop changes in behavior and personality as the disease progresses. Longitudinal studies of community-dwelling individuals with dementia reported up to 97% are affected by at least one symptom, most commonly depression or apathy, and about one third of patients had delusions, agitation, and aberrant motor behavior.[1.2.4a] Another study reported more than half of the patients with dementia will develop psychosis. The overall prevalence of delusions and hallucinations in patients are 30%, 15%, 10%, 50% and 75% for AD, VaD, FTD, PDD, DLB respectively.[1.2.4b] Neuropsychiatric symptoms are associated with greater impairment in activities of daily living, reduced quality of life, earlier institutionalization, accelerated disease progression, increased mortality, caregiver stress, and increased care cost.

Clinical Approach of Psychotic Symptoms in Neurocognitive Disorders

The goal of the history and physical examination is to establish priorities regarding the nature and urgency of interventions, characterize the signs and symptoms, identify potentially reversible exacerbating factors and create a baseline for measuring the effectiveness of treatment.

The differential diagnosis of dementia-related psychosis can be categorized into 4 groups:

1. Psychiatric illnesses such as bipolar affective disorder, late-life delusional disorder, depression with psychosis and late onset schizophrenia
2. Medications such as anti-parkinsonian drugs, anti-cholinergics, sedative-hypnotics, corticosteroids, anti-arrhythmic agents, opiates and alcohol including withdrawal
3. Medical comorbidities such as urinary tract infection, delirium, Parkinson's disease, brain lesion such as stroke, tumor, and temporal lobe epilepsy
4. Physical conditions such as pain, dehydration, hypo- or hyperglycemia, hypo- or hyperthyroidism, sodium or potassium imbalance, B12 deficiency and sleep deprivation

Schizophrenia such as psychosis can be diagnosed after exclusion of cognitive disorder, mood disorder, or other explanatory medical conditions such as delirium or focal brain pathology. Table 3 compares the characteristics between dementia-related psychosis and late-life schizophrenia.

	Dementia-Related Psychosis	Late-Life Schizophrenia
Gender	Male and female equally affected	Female predominance
Characteristics		Characterized by positive symptoms (e.g. hallucinations, delusions, and thought disorder) and negative symptoms (e.g. social dilapidation and apathy)
Hallucinations	Mostly visual hallucinations Auditory hallucinations rare	Mostly auditory hallucinations Multimodal hallucinations present
Delusions	Bizarre delusions rare Delusion misidentifications common Delusion may be paranoid or persecutory (e.g. people stealing things, spouse unfaithful)	Bizarre delusions frequent Delusion misidentification rare Prominent persecutory (paranoid) delusions
First rank symptoms	Rare	Common
Course of psychosis	Unknown, symptoms might progress with time	Eventually stabilizes and can ameliorate with time
Social interaction	Progressive deterioration; disinhibition and socially inappropriate behavior are the predominant features in FTD	Deterioration before reaching a plateau; social withdrawal and isolation are the predominant features
Cognitive function	Progressive deterioration	Deterioration before reaching a plateau
Insight	Poor	Poor
Suicidality	Rare	Frequent
Past history	Rare	Common (~85% of older adults with schizophrenia experienced onset of illness in early adulthood) Late onset schizophrenia with onset between 40-60 years; very late onset schizophrenia with onset after 60 years) – thought disorder less common, social deterioration and dilapidation rare, personality intact, fewer hallucinations and delusions, increased risk of suicidality
Anti-psychotic response	Unknown	Good
Anti-psychotic dose	Low	Moderate
Remission	Frequent	Uncommon
Need of maintenance	Rare	Common

Table 3. Characteristics between dementia-related psychosis vs. late-life schizophrenia.

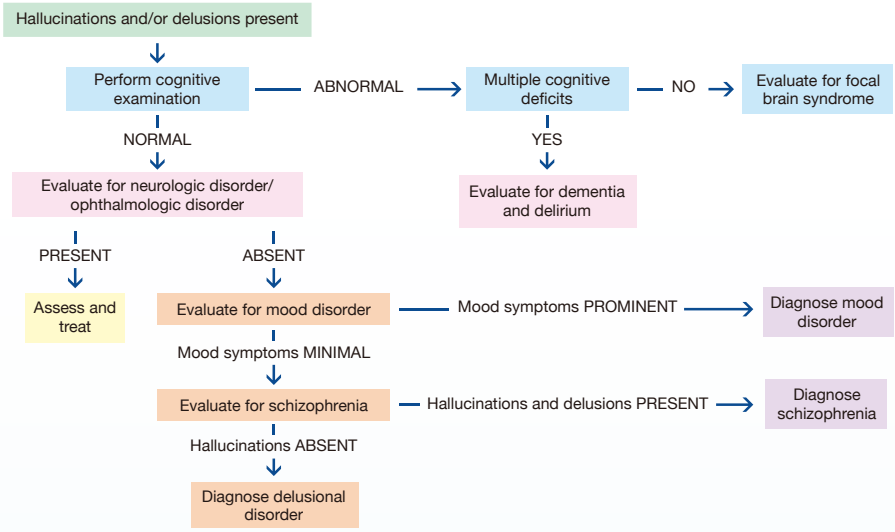


Figure 2. Evaluating an older adult with hallucination or delusion, or both (adopted from [1.2.4c]).

Assessing the Severity of Dementia-related Psychosis

The Neuropsychiatric Inventory (NPI) is useful assessment tool completed by caregivers on 12 behavioral domains commonly affected in patients with dementia. Besides, Scale for Assessment of Positive Symptoms, sections for Hallucinations and Delusions (SAPS-HD) and Behavioral Pathology of Alzheimer's Disease (BEHAVE-AD) are two focused tools for presence of symptoms and rating severity. Please refer to Section 3: Assessment Scales in Neurocognitive Disorders for details.

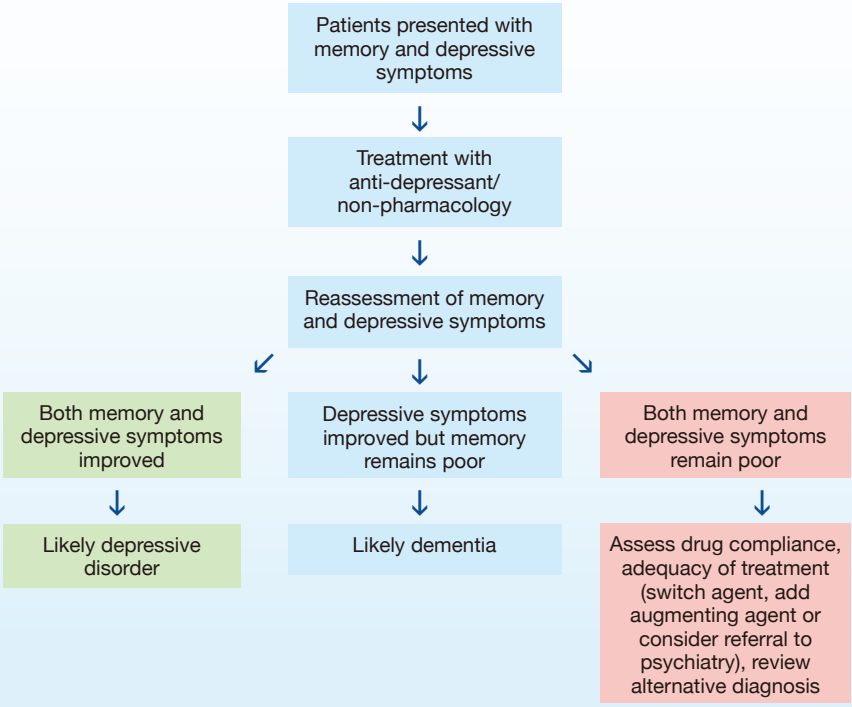
Depressive Symptoms in Neurocognitive Disorders

Patients with dementia of any type have a high incidence of major depression. The symptoms and signs of depression in dementia are often no different from major depression occurring in any other group. Hence, diagnosis of dementia with depression could not be certain until the depressive episode has remitted or at least improved. The incidence of depression is around 30% in VaD and AD and over 40% in the dementia associated with Parkinson's and Huntington's diseases. [1.2.4d]

Depression can occur in three different stages in relation to the process of neurodegeneration in dementia. Initially, it can be a predisposing risk factor occurring before the onset of dementia. The next stage it might be an early sign or prodrome of dementia and finally, it may occur at advanced stage of dementia. In each stage, depression is an important accelerating factor contributing to the clinical progression and conversion from a preclinical state to mild cognitive impairment and to dementia.

Clinical Approach of Depressive Symptoms in Neurocognitive Disorders

When an older adult presented with a significant decline in cognition and function, the differential diagnosis must include dementia and a depressive disorder. These are not mutually exclusive. So, the approach involves an adequate trial of treatment for depression.



The Symptoms and Signs of Depression in Dementia

- Low mood is most common but can be irritable, angry, or anxious.
- Disturbed biological rhythms in sleep, appetite and energy.
- May be negative, hopeless or even nihilistic. Ideas of worthlessness, guilt and self-harm also occur.
- Overall cognitive ability may decline significantly due to depression alone and only be distinguished from dementia by a trial of anti-depressant.
- Some signs of dementia may strongly resemble those of a major depression such as social withdrawal, lack of interest in self or others, low initiative and poor motivation.
- Patients may be essentially negative and depressive. Therefore, a recent change must be explored. This may only be revealed by reliable family informants.

	Dementia	Depression/Pseudodementia
Onset	Insidious (months to years)	Sudden (weeks to months)
Progression	Chronic, with slow deterioration over time	Rapid, responds to treatment
Patient history	Few details	Detailed
Mood	Fluctuates	Low/apathetic
Memory	Impaired, cueing not helpful	Improved with cueing
Attention	Usually good effort on testing	May be poor effort on testing
Orientation	Confused and disoriented, becomes lost in familiar locations	Know the correct time, date and where he/she is
Self-awareness	Likely to hide or be unaware of cognitive deficits	Likely to be concerned about memory impairment
Basic ADL	May be intact early, impaired as disease progresses	May neglect basic self-care
Instrumental ADL	May be intact early, impaired before ADLs as disease progresses	May be intact or impaired

Table 4. Characteristics between dementia with depressive symptoms vs. major depression or pseudodementia.

Examples of rating scales for depression validated in older adults are Geriatric Depression Scale and Cornell Scale for Depression in Dementia. Please refer to Section 3: Assessment Scales in Neurocognitive Disorders for details.

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1.2.5 Gait Disturbance in Neurocognitive Disorders

Cognitive decline and neurodegenerative disease have been implicated in gait dysfunction. As cognition declines, gait velocity decreases, variability increases and ability to multitask while walking is impaired. [1.2.5a]

Gait speed and gait disturbance are important in the assessment of patients with neurocognitive disorders. Slow gait speed is a predictor of negative outcomes (e.g. falls and disability) in older adults and in those at risk to develop cognitive impairment. Slow gait speed and gait abnormality predict incident MCI and dementia. The presence of unsteady, hemiparetic or frontal gait pattern was associated with more than a threefold increased risk of developing VaD within 3 years. Patterns of quantitative gait impairment might also differentially predict AD vs. VaD. [1.2.5a] [1.2.5b]

Motoric cognitive risk syndrome (MCR) is a pre-dementia syndrome that could be diagnosed without requiring cognitive tests or specialized equipment. It is defined as the presence of slow gait (1 SD below age- and sex-matched peers) and cognitive complaint and serves as a clinical biomarker for high risk of neurologic decline (all-cause dementia, VaD and AD). [1.2.5a]

Gait Disturbance in Different Dementia Subtypes [1.2.5a]

Alzheimer's dementia: Alzheimer's dementia was traditionally thought to have a normal gait. However, studies have found that gait disturbance is actually common in AD. As dementia progresses, changes to walking and other motoric abilities continue that eventually lead to mobility loss and being bedridden. Patients with AD typically have quantitative gait impairment while those with other forms of dementia often manifest more overt, qualitative changes to walking.

VaD commonly results in hemiparetic, frontal or ataxic gaits. NPH results in a frontal gait. FTD does not typically feature a frontal gait but gait abnormalities have been described. FTD can cooccur with amyotrophic lateral sclerosis (ALS). A variety of gait patterns can be seen depending on the pattern or upper- and lower-motor neuron involvement.

PDD typically presents with a classic Parkinsonian gait. PSP and vascular parkinsonism may have a wider base or a more "frontal" appearance and may be associated with other neurologic abnormalities involving eye movements, balance or limb positioning. CBD may have variable gait dysfunction depending on the limb(s) involved and the specific symptoms present (e.g. dystonia or parkinsonism).

Clinical Approach

History: The presenting history can provide diagnostic clues. An insidious onset suggests a degenerative disorder while a sudden stepwise progression suggests a cerebrovascular disease. Reported pain in the neck, low back or lower extremities suggests degenerative musculoskeletal conditions. Gait abnormality with urinary urgency and incontinence suggests multiple cerebral infarcts, Binswanger's disease, NPH or cervical spondylotic myelopathy. A history of alcohol and medication intake may be helpful in establishing the diagnosis. Benzodiazepines, phenytoin and neuroleptic drugs are known to affect, respectively, the vestibular system, cerebellum and basal ganglia. Toxic/metabolic causes of gait abnormality are important to identify because they are generally reversible. Symptoms of depression should be elicited because depressed patients may exhibit slowness from psychomotor retardation, manifesting as a lack of purpose in stride and a lifting action of the legs during gait. In the setting of a gait disorder and recent fall, the fall nature should be carefully evaluated. Falling stiffly backward is common in Parkinson's disease and loss of strength from a transient ischemic attack. The location and activity of patient during the fall may point to environmental or patient-related causes (orthostatic hypotension for falls shortly after patient arisen from sitting or lying down, post-prandial hypotension for falls shortly after meals). Recurrent tripping may be caused by a foot drop or increased tone from spasticity. [1.2.5c]

Physical examination: Most revealing features of a patient's gait can be gathered by careful systematic observation alone. The gait examination begins by observing the patient as he or she rises from the chair to stand. The ease of the transition and the standing posture should be noted. A flexed posture can be a sign of Parkinson's disease or lumbar spinal stenosis. The width of the feet during stance can be a sign of imbalance, seen in frontal lobe disease, cerebellar ataxia, sensory ataxia and cervical spondylotic myelopathy. Standing balance in single leg stance and in tandem stance should be observed. Next, with the patient comfortably standing, ask the patient to close his or her eyes (Romberg's test) to differentiate sensory ataxia (standing imbalance aggravated by eye closure) from cerebellar ataxia. The clinician should remain close to the patient in case he or she begins to fall. The patient is then asked to walk at a normal pace. Difficult initiation can indicate Parkinson's disease or frontal lobe disease. Once the walking is under way, the patient is observed from the side, front and back. The overall pattern of body movement should first be noted. Next, the patient should be observed from the feet upward, with the observer

relating the action of the two limbs, the torso and then the upper extremities. The observer should be able to differentiate a focal problem in an extremity to a generalized movement disorder. The velocity, step length, step width, rhythm and cadence all should be noted. The fluidity and symmetry of arm swing should be noted, as should the use of any assistive devices. Asking the patient to walk at a faster pace may elicit more subtle gait abnormality. Tandem walk and the heel-to-shin test often bring out subtle cerebellar and sensory ataxias. The remaining routine neurologic and musculoskeletal examinations should focus on evaluating muscle bulk and strength, sensation, proprioception, deep tendon reflexes, spinal deformity, limb-length inequalities, and joint motion. Finally, brief screening examinations of vision and hearing should be performed. [1.2.5c]

Common neurologic gait disorders in neurocognitive disorders include (1) frontal (apraxic) gait; (2) Parkinsonian gait; (3) hemiparetic gait; and (4) ataxic gait. [1.2.5a] [1.2.5c] [1.2.5d] [1.2.5e] [1.2.5f]

Frontal (apraxic gait) (higher level gait disorders due to dysfunction in frontal lobe(s) and related network) is characterized by (1) cautious slow gait (shortened stride length on a normal or slightly wide base, may have hesitation, freezing, en bloc turns, and magnetic gait); (2) gait ignition failure (difficulty initiation); (3) frontal disequilibrium (inappropriate or counterproductive postural and locomotion responses; easily displaced backwards, precipitating falls); and (4) frontal ataxia (wide-based and lurching gait that resembles cerebellar ataxia). Other associated clinical features include frontal release signs, executive dysfunction, depression and frequent falls. Classic frontal gait may mimic Parkinsonian gait but frontal gait lacks other signs of Parkinsonism (e.g. resting tremor, bradykinesia and mask face).

Parkinsonian gait (due to diseases of basal ganglia) is characterized by shuffling (narrow base with reduced stride length, reduced step height, slow speed, rigidity), stooped posture, reduced arm swing, festinating (center of gravity thrown forwards and take increasing faster, short (petit pas) steps in a hurry), difficulty initiation, hesitation and freezing (walking stops when stepping through a doorway or during turning). Other associated clinical features include hypokinetic-rigid features (e.g. resting tremor, bradykinesia).

Hemiparetic gait presents with circumduction gait with upper motor neuron leg and arm weakness and posturing.

Cerebellar ataxic gait (due to cerebellar lesion) presents with a wide-based gait with irregular, unsteady, staggering, sudden lurching to either side, forward or backward like being drunk. Other associated clinical features include dysarthria, hypermetria and nystagmus. Romberg's sign is negative (not aggravated by eye closure). Sensory ataxic gait (due to loss of proprioception) presents with a wide-based, high stepping gait (which constantly observes the foot position). Romberg's sign is positive (aggravated by eye closure).

Assessment of neurologic gait disorders in patients with neurocognitive disorders can provide diagnostic clues to the dementia subtypes as follows:

Neurologic Gait Disorder	**Dementia Subtypes Commonly Affected** (not exhaustive)
Frontal (apraxic) gait	VaD (due to small vessel disease) NPH Other neurodegenerative diseases affecting frontal lobes (e.g. FTD, parkinsonian syndromes and AD – cautious gait if mild, frontal gait if severe)
Parkinsonian gait	LBD (PDD and DLB) Other Parkinsonian syndromes (PSP, CBD, multiple system atrophy (MSA), drug-induced parkinsonism, vascular parkinsonism – preferentially affect lower body)
Hemiparetic gait	Vascular dementia (due to cerebrovascular accident)
Ataxic gait	Cerebellar: VaD, alcohol-related, spinocerebellar ataxia, paraneoplastic diseases, prion diseases (esp. familial and variant CJD), mitochondrial disorders, MSA, etc. Sensory: tabes dorsalis (syphilis), vitamin B12 deficiency, polyneuropathy (diabetes, HIV, neurotoxic medications), etc.

In older adults, gait disorders are frequently multifactorial in origin. Non-neurologic causes (e.g. visual/hearing impairment, musculoskeletal problems, pain, side effects of medications, cardiorespiratory problems esp. orthostasis) should not be overlooked and may be mixed with neurologic causes.

We should evaluate the involvement of cognitive domains, motor symptoms and neurological signs, behavioral and neuropsychiatric symptoms, and comorbid medical conditions. Significant positive findings guide us to the appropriate potential diagnosis. Please refer to Section 1.1.3: Pattern Recognition in Different Subtypes of Major Neurocognitive Disorders for details. Further laboratory and radiological investigation should follow the protocol of global cognitive impairments. Please refer to Section 4: Investigation – Neuroimaging and AD Biomarkers for details.

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1.2.6 Parkinsonism in Neurocognitive Disorders

Parkinsonism is a disorder characterized by the clinical tetrad of resting tremor, rigidity, akinesia, and postural instability.

Dementia syndromes associated with parkinsonism includes (not exhaustive):

- Neurodegenerative diseases: PDD, DLB, AD, Parkinson plus syndromes and FTD.
- Secondary parkinsonism: vascular parkinsonism and dementia, drug-induced parkinsonism and NPH

Rigidity and postural instability develop in roughly 30% of patients with AD.

The "1-year rule" discriminates the temporal relationship between PDD from DLB and AD.

While, early stage DLB has significantly more prominent parkinsonism compared with similar stage of AD.

- PSP: In the vast majority of cases, Richardson's syndrome, are characterized by prominent postural instability, supranuclear vertical gaze palsy and frontal dysfunction. Cognitively, the executive functions, attention, and free recall memory are impaired. Psychotic symptoms such as hallucination and delusion are uncommon compared with PDD or DLB but apathy and anhedonia, disinhibition, depression, and bulbar affect are common.
- CBD: The relatively rare parkinsonian dementia syndrome is classically characterized by asymmetrical presentation of limb rigidity, akinesia, dystonia, myoclonus, orobuccal or limb apraxia, cortical sensory deficit, or alien limb phenomena. The cognitive profiles are variable depend on the topographic pattern of pathology. The psychiatric disturbances are similar to PSP.
- MSA: It is characterized by a variable combination of parkinsonism (MSA-P), cerebellar ataxia (MSA-C), and/or autonomic dysfunction. Cognitive dysfunction is an exclusion criterion for the diagnosis of MSA in some well validated clinical criteria.

- FTD: In contrast to progressive non-fluent aphasia (PNFA) and bvFTD, semantic dementia rarely manifests with parkinsonism. Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) of microtubule-associated protein tau gene (MAPT) and progranulin gene (GRN) have autosomal dominant pattern of inheritance. Parkinsonism has been reported in up to 30% of C9orf72 genetic mutation FTD.
- Vascular Parkinsonism: VaD and vascular parkinsonism are overlapping spectrums of cognitive and extrapyramidal manifestations associated with subcortical vascular damage. VaD and vascular parkinsonism can also present in other neurodegenerative diseases. Vascular parkinsonism starts to occur around 70 years of age and is characterized by subcortical dementia, gait apraxia, lower body parkinsonism and absence of non-motor symptoms of Parkinson's disease.
- Drug-induced parkinsonism and dementia: Dopamine D2 receptor antagonist, such as anti-psychotics or anti-emetics, can cause drug-induced parkinsonism. Some may use anti-cholinergic agent to treat, however, it will exacerbate cognitive impairment.

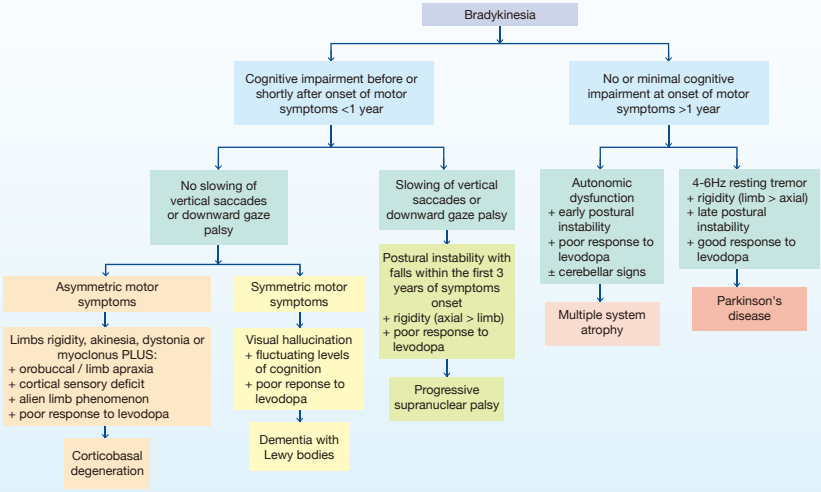

Figure 3. Approach to differential diagnosis of atypical parkinsonism. [1.2.6a]

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1.2.7 Young-Onset Dementia

- Referred to the group of progressive neurodegenerative diseases which commonly affect individuals before 65 years of age.
- Can be hereditary, multifactorial, sporadic.
- More likely to have a genetic cause, or may be adult-onset forms of metabolic disorders which include dementia.
- Can exist as a primarily cognitive state or be part of a larger syndrome. [1.2.7a]

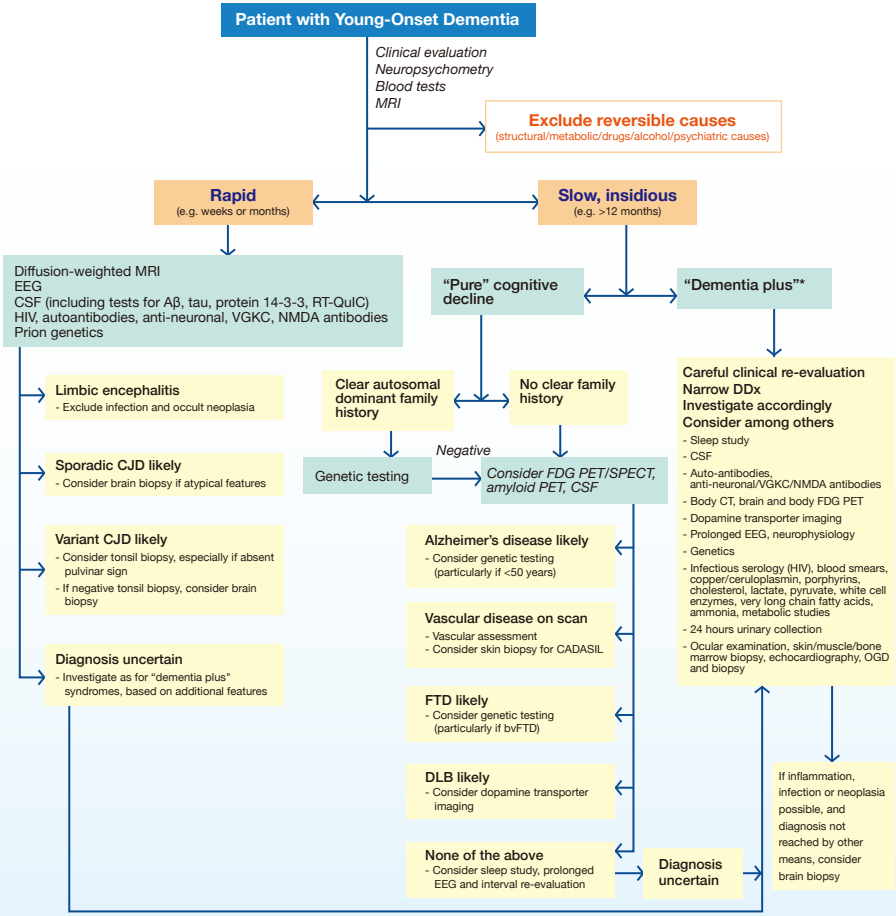
Categories of young-onset hereditary dementias		
Hereditary Primary Dementias	**Hereditary Movement Disorders with Dementia**	**Hereditary Metabolic Diseases with Dementia**
Alzheimer's disease	Huntington's disease	Adult Tay-Sachs disease
Frontotemporal dementia	Spinocerebellar ataxias	Kufs disease
Prion diseases	Dentatorubral-pallidoluysian atrophy	Adrenoleukodystrophy
CADASIL		Metachromatic leukodystrophy
Lewy body dementia (rarely hereditary)	Parkinson's disease dementia	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, and other mitochondrial diseases
Other vascular dementias	Neuroacanthocytosis	Krabbe disease
		Fabry disease
		Niemann-Pick type C disease
		Wilson's disease
		Adult polyglucosan body disease
		Cerebrotendinous xanthomatosis

Table 5. Categories of young-onset hereditary dementias. [1.2.7a]

SECTION 1

First Time Assessment and Clinical Diagnostic Approach of Different Presentations in Neurocognitive Disorders

Clinical Approach for Assessment and Investigation of Young-Onset Dementia [1.2.7b]



*Dementia plus syndromes are dementia syndromes in which cognitive impairment is accompanied by additional neurological or systemic features.

Neurological features include pyramidal signs, akinetic-rigid syndrome, ataxia, dystonia/chorea, myoclonus or early seizures, bucco-lingual mutilation, peripheral neuropathy, dysautonomia, gaze palsy, deafness

Systemic features include cataracts, splenomegaly, tendon xanthomas, bone cysts, Paget's disease, renal impairment, hepatic dysfunction, respiratory failure, gastrointestinal dysfunction, anemia, skin lesions, metabolic or infectious crises, hyponatremia. [1.2.7b]

References

[1.2.7a] Goldman JS. Genetic testing and counseling in the diagnosis and management of young-onset dementias. Psychiatr Clin North Am. 2015 Jun;38(2):295-308.

[1.2.7b] Rossor MN, Fox NC, Mummery CJ, et al. The diagnosis of young-onset dementia. Lancet Neurol. 2010 Aug;9(8):793-806.

1.2.8 Rapidly Progressive Dementia

Definition: There is no clear definition for the time frame of a rapidly progressive dementia (RPD). However, it is generally defined as a loss of cognitive function hyperacutely (over days or weeks), subacutely (over months or 1-2 years), or more than expected with a known dementia syndrome.

The potential causes of RPD are extensive, emphasizing the need for a systematic approach. One useful mnemonic VITAMINS can help remembering the differential diagnosis: namely: Vascular, Infectious, Toxic-metabolic, Autoimmune, Metastases, Iatrogenic, Neurodegenerative, and Systemic causes.

From 5 largest case series, definitive cause of RPD was identified in 95.4% of patients. CJD represented the most common diagnosis (58.5%), followed by neurodegenerative diseases (22.5%), while 18.8% were potentially treatable conditions. Therefore, attention must be directed to identifying potentially reversible causes of RPD.

Initial RPD screening includes blood and urine tests to rule out a simple metabolic perturbation or infection screen, CSF analysis, brain MRI and EEG. It is followed by second tier RPD workup depending on the initial RPD screening and clinical scenario.

For most RPDs, it is generally recommended a basic autoimmune screen, followed by autoimmune/paraneoplastic antibodies panel in suspected cases.

Features of autoimmune encephalopathy includes: subacute onset, fluctuating course, tremor, headache, personal or family history of autoimmunity, history of recent or past neoplasia, evidence of CNS inflammation on CSF (e.g. elevated protein, pleocytosis, oligoclonal bands), evidence of CNS inflammation on MRI (mesial temporal or other regional T2 hyperintensity), hypometabolism on functional imaging, detection of neural autoantibodies (e.g. ANNA Ab, VGKC complex Ab, NMDA receptor Ab, etc.).

Numerous vascular conditions can cause RPDs, including strokes or multiple infarcts, cerebral angiopathy, dural arteriovenous fistulas, and hypertensive encephalopathy. Any vascular disruption of the thalamus, especially if bilateral involvement, such as through venous thrombosis, can result in an RPD.

Non-prion neurodegenerative disease can present as RPD but usually with a slower course. Caregivers may underestimate the duration of illness due to a tendency to equate major incidents with the onset of disease.

There are 3 different etiologies of CJD: sporadic (85%), genetic (10-15%), and acquired (<1%). Sporadic CJD is characterized by progressive dementia, cerebellar or visual disturbance, myoclonus, pyramidal or extrapyramidal symptoms and akinetic mutism.

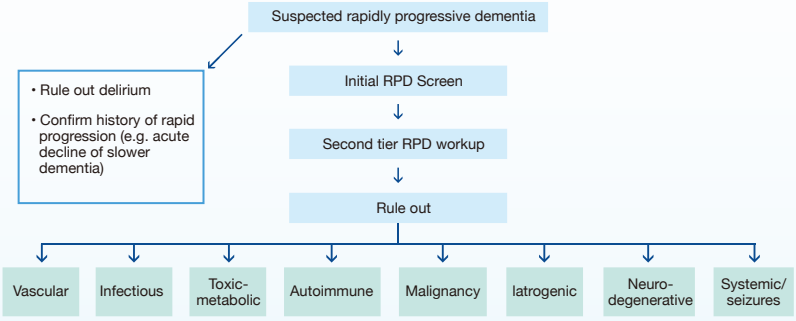


Figure 4. Algorithm for evaluating RPD. [1.2.8b]

Vascular	Multi-infarct, thalamic or callosum infarct, cerebral amyloid angiopathy, dural arteriovenous fistulas, CNS vasculitis, venous thrombosis
Infectious	HSV, HIV, fungal, syphilis, parasites, Whipple's disease, urinary tract infection or pneumonia in frail elderly
Toxic-metabolic	B12/B1/B3 deficiency, uremia, Wilson's disease, porphyria Heavy metal toxicity (bismuth/lithium/mercury/arsenic) Endocrine - thyroid, parathyroid, adrenal
Autoimmune	Antibody-mediated encephalopathy, CNS lupus, acute disseminated encephalomyelitis, Hashimoto encephalopathy, other CNS vasculitides
Metastases/Neoplasm Related	Paraneoplastic diseases (limbic encephalopathy), primary CNS lymphoma, intravascular lymphoma
Iatrogenic	Medication toxicity (lithium, methotrexate, chemotherapy), illicit drug use
Neurodegenerative	CJD, CBD, PSP, FTD, AD, DLB
Systemic	Sarcoidosis, epilepsy, non-convulsive status epilepticus, mitochondrial disease

Table 6. Differential diagnosis of RPD (not exhaustive). [1.2.8b]

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[1.2.8b] Geschwind MD. Rapidly Progressive Dementia. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):510-37.

[1.2.8c] McKeon A. Autoimmune Encephalopathies and Dementia. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):538-58

1.2.9 Hereditary Dementia

Most common hereditary dementias include AD, FTD, Huntington's disease (HD), prion diseases, and CADASIL. [1.2.9a] [1.2.9b]

Familial AD (PSEN1, PSEN2, APP; APOE) and FTD (MAPT, GRN, CHMP2B for FTD; C9orf72, TARDBP, FUS for FTD-ALS) have several causal genes and genetic risk factors whereas HD (HTT), prion diseases (PRNP), and CADASIL (NOTCH3) are single-gene disorders. [1.2.9a] [1.2.9b]

Clinical Approach for Genetic Testing of Patients with Suspected Hereditary Dementia [1.2.9b]

For Patients with Suspected Hereditary Dementia

↓

Please assess:

1. Clinical presentation (memory problem vs. non-memory problem; to determine the dementia subtype)
2. Age of onset (early onset <65 years vs. late onset >65 years)
3. Family history [1.2.9a][1.2.9b] (can use modified Goldman score)*
   - Obtain three-generation family pedigree (age of onset, current age, age of death)
   - Neurological or psychiatric condition explored
   - Non-cognitive features (cerebral amyloid angiopathy, spastic paraplegia, seizures for AD; ALS for FTD-ALS; stroke-like symptoms, migraine with aura for CADASIL; sleep/visual abnormalities, cerebellar signs, movement disorders (parkinsonism, dystonia, myoclonus), seizures for prion diseases; movement disorder for HD)

*Modified Goldman Score [1.2.9c] (to determine the degree of autosomal dominant inheritance)

1.	Autosomal dominant family history (at least 3 affected people in 2 generations with 1 person being a first-degree relative of the other 2)
2.	Familial aggregation of 3 of more family members with dementia but not meeting criteria for 1
3,3.5	1 other affected family member with dementia (modified to give a score of 3 only if there is a history of young-onset dementia within the family, i.e. less than 65 years, and 3.5 if onset above 65 years)
4	No or unknown family history

↓

Consider/Offer Genetic Testing	Generally No Genetic Testing
• AD with a strong family history • AD with family history of early onset dementia • Early onset AD • bvFTD or FTD-ALS • FTD-PPA or FTD-CBD with a strong family history • HD or prion disease phenotype	• AD with age of onset >65 years • PPA with no strong family history • Atypical parkinsonian syndromes

Genetic testing requires genetic counselling and informed consent.[1.2.9b] Bear in mind that there are possible detrimental effects on psychosocial, job and insurance prospects. Genetic tests for hereditary dementias can be available in local genetic laboratories in Hong Kong.

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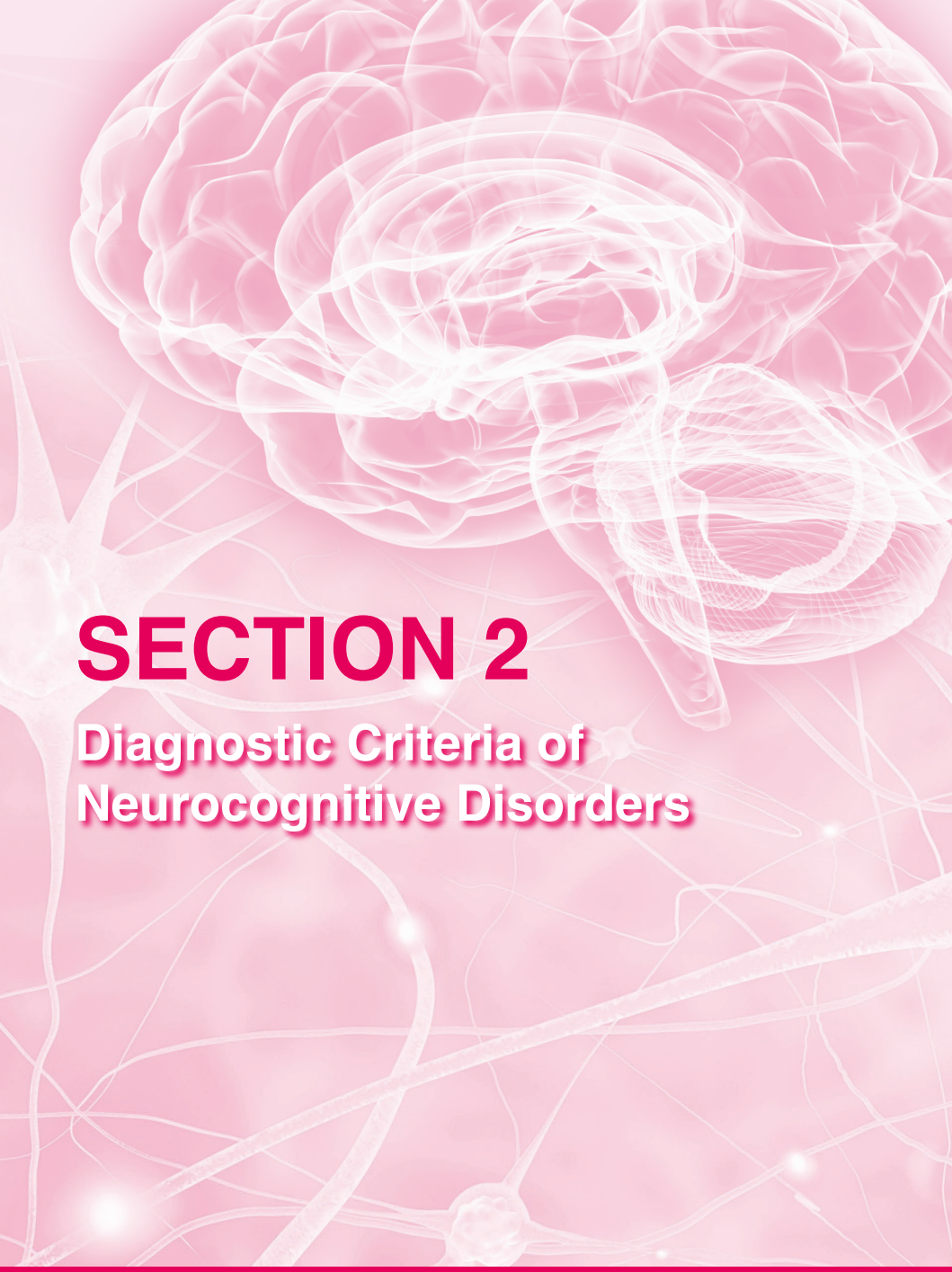

SECTION 2

Diagnostic Criteria of Neurocognitive Disorders

SECTION 2

Diagnostic Criteria of Neurocognitive Disorders

2.1 Dementia/Major Neurocognitive Disorder (Major NCD)

2.1.1 DSM-5 Criteria for Major Neurocognitive Disorder 2013 [2.1a]

Major Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
   2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e. at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

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

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

2.1.2 NIA-AA Criteria for All-Cause Dementia 2011 [2.1b]

When cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history taking from patient and a knowledgeable informant and (2) an objective cognitive assessment, either a bedside mental status examination or neuropsychological testing.
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
   a. Impaired ability to acquire and remember new information
   b. Impaired reasoning, handling of complex tasks and poor judgment
   c. Impaired visuospatial abilities
   d. Impaired language functions
   e. Change in personality, behaviour, or comportment

2.1.3 Practical Notes on All-Cause Dementia [2.1c]

DSM-5

DSM-5 has extensively revised the diagnostic criteria and approach in neurocognitive disorders (NCDs), which referred to in DSM-4 as "Dementia, Delirium, Amnestic, and Other Cognitive Disorders".

The choice of a new term "NCD" for "dementia" is based on the rationale that this disorder is not restricted to older adults. It is often a preferred term for conditions affecting younger individuals, such as NCD due to HIV infection. The prefix "neuro" represents the "structural brain" while "cognitive" alone has been understood as "psychological mind". The addition of "neuro" will define the disorder belongs to structural brain diseases and not a "mind disorder".

DSM-5 adopts a multi-step approach in the classification of neurocognitive disorders.

Major or Mild NCD

First is to exclude delirium and then decide whether it is a major or mild neurocognitive disorder. A single domain being affected (cognitive impairment being concerned AND documented by neuropsychological testing or quantified clinical assessment) is adequate to be classified as NCD. The distinction between major and mild depends on how significantly it interferes with the independence in everyday activities and the degree of impairment in objective testing. Major NCD has substantial impairment with the test performance in the range of two or more standard deviations below appropriate norm (below the 3rd percentile), whereas mild NCD has modest impairment with performance lies in 1-2 SDs range below the mean (between the 3rd and 16th percentiles).

The six cognitive domains listed in DSM-5 for establishing the presence of NCD are:

- Complex attention: sustained attention, divided attention, selective attention and information processing speed
- Executive function: planning, decision making, working memory, responding to feedback, inhibition and mental flexibility
- Learning and memory: free recall, cued recall, recognition memory, semantic and autobiographical long-term memory, and implicit learning

- Language: object naming, word finding, fluency, grammar and syntax, and receptive language
- Perceptual-motor: visual perception, visuo-constructional reasoning and perceptual-motor coordination
- Social cognition: recognition of emotions, theory of mind and insight

Examples of symptoms or observations regarding impairments in everyday activities, and examples of assessments are also listed in the DSM-5. They are useful in guiding the clinical approach and may help in selecting fast and practical tests in memory clinics.

Etiological Subtypes

After determination of major or mild NCD, it follows by subtyping into various etiological groups which include:

1. NCD due to Alzheimer's disease*
2. Vascular NCD*
3. NCD with Lewy bodies*
4. NCD due to Parkinson's disease*
5. Frontotemporal NCD*
6. NCD due to traumatic brain injury
7. NCD due to HIV infection
8. Substance/medication induced NCD
9. NCD due to Huntington's disease
10. NCD due to prion disease
11. NCD due to another medical condition*
12. NCD due to multiple etiologies*
13. Unspecified NCD

Note that all can be classified as major or mild. The etiological subtyping is linking up with the world expert panel criteria in each disorder. For example, mild NCD due to Alzheimer's disease (AD) will be broadly similar to mild cognitive impairment (MCI) in the Petersen criteria. However, it demands an additional objective assessment. Also note that major NCD due to AD requires two domains, one of which needs to be memory. Therefore, it still adheres to the convention. In addition, the DSM-5 criteria due to different subtypes also adopt probable and possible classification in line with world expert panel criteria. This is another major difference from DSM-4.

The * are more important for older adults and can be referred to the different sections of this manual. As remarked in the DSM-5 manual, older adults are commonly complicated by comorbidities, which make subtyping difficult.

Specifiers

After subtyping, we can assign specifiers, which are similar to behavioral and psychological symptoms of dementia, and they are listed below:

- Delusions
- Hallucinations
- Mood disturbance
- Agitation
- Combative behaviors
- Sleep disturbance
- Apathy

This is a good list for history taking and mental examination. It helps to identify non-cognitive problems in dementia that needs either pharmacological or non-pharmacological intervention.

DSM is a classification manual for mental disorders and is not intended to replace the clinical approach for the diagnosis of diseases. Although it may provide a "checklist" for the clinical features of the disorder, it itself is neither sufficient nor necessary to establish a diagnosis. Ultimately, the diagnosis of NCD or dementia is based on clinical judgment and may include considerations outside the criteria. It is only an "assistant" in clinical practice and a "common language" for communication among clinicians and researchers.

NIA-AA

- NIA-AA combines with clinical (cognitive) and research (biomarkers) criteria, while DSM-5 focuses exclusively on clinical diagnosis. NIA-AA guidelines are mainly for AD diagnosis, while DSM-5 includes diagnostic criteria for various subtypes of NCD.

References

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2.2 Mild Cognitive Impairment (MCI)/Mild Neurocognitive Disorder (Mild NCD)

2.2.1 DSM-5 Criteria for Mild Neurocognitive Disorder 2013 [2.2a]

Mild Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

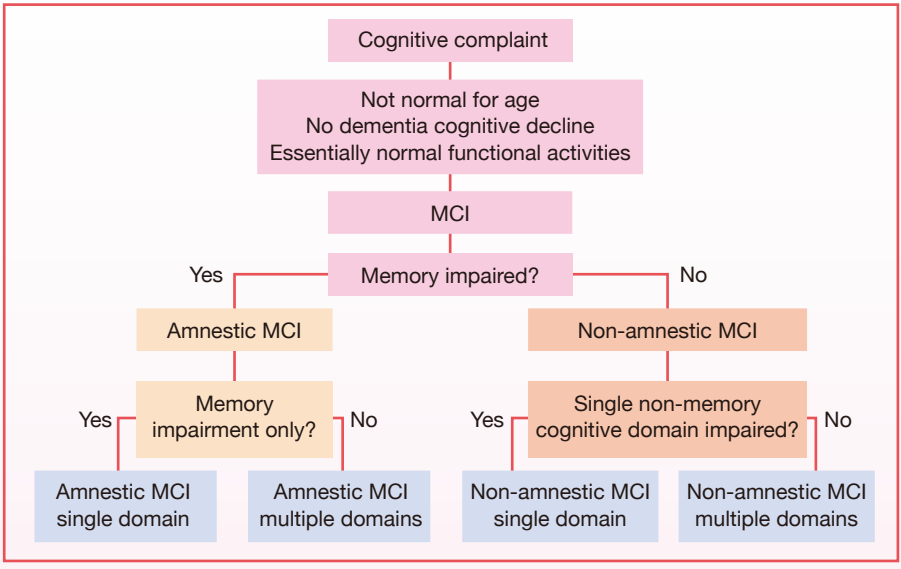
B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e. complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required.

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

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

2.2.2 International Working Group (IWG) on MCI Criteria 2004 [2.2b]

- Presence of a cognitive complaint from either the subject and/or a family member
- Absence of dementia
- Change from normal functioning
- Decline in any area of cognitive functioning
- Preserved overall general functioning but possibly with increasing diffculty in the performance of activities of daily living
- Sub-classifed to amnestic or non-amnestic; single domain or multiple domain



2.2.3 Petersen Criteria for MCI 1999 [2.2c]

- Presence of a subjective memory complaint
- Preserved general intellectual functioning
- Demonstration of a memory impairment by cognitive testing
- Intact ability to perform activities of daily living
- Absence of dementia

2.2.4 Practical Notes on MCI

The concept of MCI has been developed since 1999 with the classical Petersen criteria for MCI. The diagnosis is made when there is a memory impairment inconsistent for their age, and that the deficit does not interfere significantly with their daily activities. It is often considered to be the boundary or transitional stage between normal aging and dementia, and interventions like cognitive rehabilitation and memory training may delay this progression. The annual conversion rate of amnestic MCI to Alzheimer's dementia is approximately 5-10%.

The 2004 International Working Group on MCI criteria included the component of increasing difficulty in performing everyday tasks without the loss of autonomy, like changes in the areas of dressing, use of telephone, money and household appliances. In addition, it also included cognitive deficits other than memory and sub-classified MCI into amnestic or non-amnestic, and single or multiple domain types.

In 2009, Jak and colleagues further classified MCI into four neuropsychologically distinct clusters, including amnestic, mixed, dysexecutive and visuospatial. This is a comprehensive neuropsychological classification system for identification of multiple subtypes of MCI.

In the updated criteria of DSM-5 published in 2013, the term mild NCD is used to recognize this less severe level of cognitive impairment and disabling syndromes. It is broadly equivalent to MCI. The diagnostic criteria states that there should be evidence of modest cognitive decline in one or more cognitive domains, but do not interfere with capacity for independence in daily functioning, i.e. the person can still perform complex instrumental activities of daily living with effort or other compensatory strategies.

It is challenging to make a distinction between MCI and normal aging. MCI is mainly a clinical diagnosis, which is made mainly by detailed history from the patients and the caregivers, cognitive screening tests and the more comprehensive neuropsychological testing. Clinical Dementia Rating (CDR) scale and Global Deterioration Scale (GDS) are two useful scales to aid the diagnosis. Patients with a CDR of 0 or 0.5 or GDS stage 2 or 3 belong to group of MCI. For borderline MCI cases, neuropsychological testing can help distinguish them from normal aging. Functional imaging studies is believed to be most helpful in early detection.

Patients with MCI should be screened and treated for vascular risk factors, especially hypertension, to ameliorate the risk of cognitive decline. And they should be evaluated and treated for reversible causes of cognitive impairment, including medication side effects, sleep disturbances, depression, vitamin B12 deficiency or hypothyroidism. At present, there is no single medication having proven symptomatic or preventive benefits in MCI. Cognitive rehabilitation program and lifestyle modification, e.g. moderate degree of physical exercise, Dietary Approaches to Stop Hypertension (DASH diet) may delay cognitive decline.

2.2.5 Practical Notes on Pre-MCI Stage: Transitional Cognitive Decline (TCD), Subjective Cognitive Decline (SCD) and Mild Behavioral Impairment (MBI)

Transitional cognitive decline (TCD) is the cognitive performance in the non-impaired range but with a subjective complaint of cognitive decline, or a subtle decline measured on longitudinal cognitive testing, or neurobehavioral symptoms, or combinations of these. [2.2d]

TCD (stage 2 in numeric staging scheme in Alzheimer's continuum in 2018 NIA-AA Research Framework) is a distinct transitional stage between asymptomatic (stage 1) and mildly impaired (stage 3). [2.2d]

Subjective cognitive decline (SCD) is self-perceived decline in any cognitive domain over time (pre-MCI stage). SCD in individuals with unimpaired performance on cognitive tests (age-, gender- and education-adjusted) may represent the first symptomatic manifestation of AD. However, numerous causes of SCD other than preclinical AD exist (e.g. normal aging, personality traits, psychiatric and neurologic disorders other than AD, or related to effects of medication and substance use). So, SCD cannot be considered equal to a prodromal phase of AD (preclinical AD). SCD is associated with an increased risk of positive biomarkers for Alzheimer's pathology and later conversion to dementia. [2.2e] [2.2f]

"SCD plus" refers to a set of features that increase the likelihood of the presence of preclinical AD in individuals with SCD (e.g. subjective decline in memory, age at onset ≥60 years, onset within last 5 years, concerns/worries associated, feeling of worse performance than others of the same age group, cognitive decline confirmed by an informant, presence of APOE ε4 genotype and biomarker evidence for AD). It was showed that a significantly higher risk of developing MCI among subjects with SCD plus (18.9%) compared with SCD alone (5.6%). [2.2e] [2.2f]

Mild behavioral impairment (MBI) is a neurobehavioral syndrome characterized by new onset of neuropsychiatric symptoms (NPS) in later life (changes in behavior or personality after 50 years old). Systemic review showed that MBI is associated with a higher risk of cognitive decline in comparison to older adults without NPS. MCI patients mostly converted to AD whereas MBI patients converted mostly to frontotemporal dementia and dementia with Lewy bodies. [2.2g] [2.2h]

SECTION 2

Diagnostic Criteria of Neurocognitive Disorders

References

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2.3 Alzheimer's Disease (AD) and Dementia due to AD

2.3.1 IWG-2 Criteria for Typical AD 2014 [2.3a]

IWG-2 Criteria for Typical AD (A Plus B at any Stage)

A Specific Clinical Phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioral changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo Evidence of Alzheimer's Pathology (One of the Followings)

- Decreased $A\beta_{1-42}$ together with increased total tau (T-tau) or phosphorylated tau (P-tau) in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

Exclusion Criteria† for Typical AD

History

- Sudden onset
- Early occurrence of the following symptoms: gait disturbances, seizures, major and prevalent behavioral changes

Clinical features

- Focal neurological features
- Early extrapyramidal signs
- Early hallucinations
- Cognitive fluctuations

Other medical conditions severe enough to account for memory and related symptoms

- Non-AD dementia
- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, and metabolic disorders, all of which may require specific investigations
- MRI FLAIR or T2 signal changes in the medial temporal lobe that are consistent with infectious or vascular insults

*Hippocampal amnestic syndrome might be difficult to identify in the moderately severe to severe dementia stages of the disease, in which in-vivo evidence of Alzheimer's pathology might be sufficient in the presence of a well characterised dementia syndrome. †Additional investigations, such as blood tests and brain MRI, are needed to exclude other causes of cognitive disorders or dementia, or concomitant pathologies (vascular lesions).

2.3.2 IWG-2 Criteria for Atypical AD 2014 [2.3a]

IWG-2 Criteria for Atypical AD (A Plus B at any Stage)

A Specific Clinical Phenotype (One of the Followings)

- Posterior variant of AD (including)
  - An occipitotemporal variant defined by the presence of an early, predominant, and progressive impairment of visuoperceptive functions or of visual identification of objects, symbols, words, or faces
  - A biparietal variant defined by the presence of early, predominant, and progressive difficulty with visuospatial function, features of Gerstmann syndrome, of Balint syndrome, limb apraxia, or neglect
- Logopenic variant of AD defined by the presence of an early, predominant, and progressive impairment of single word retrieval and in repetition of sentences, in the context of spared semantic, syntactic, and motor speech abilities
- Frontal variant of AD defined by the presence of early, predominant, and progressive behavioral changes including association of primary apathy or behavioral disinhibition, or predominant executive dysfunction on cognitive testing
- Down's syndrome variant of AD defined by the occurrence of a dementia characterized by early behavioral changes and executive dysfunction in people with Down's syndrome

B In-vivo Evidence of Alzheimer's Pathology (One of the Followings)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- Alzheimer's disease autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

Exclusion Criteria* for Atypical AD

History

- Sudden onset
- Early and prevalent episodic memory disorders

Other medical conditions severe enough to account for related symptoms

- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, or metabolic disorders

*Additional investigations, such as blood tests and brain MRI, are needed to exclude other causes of cognitive disorders or dementia, or concomitant pathologies (vascular lesions).

2.3.3 IWG-2 Criteria for Mixed AD 2014 [2.3a]

IWG-2 Criteria for Mixed AD (A Plus B)

A Clinical and Biomarker Evidence of AD (Both are Required)

- Amnestic syndrome of the hippocampal type or one of the clinical phenotypes of atypical AD
- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF, or increased tracer retention on amyloid PET

B Clinical and Biomarker Evidence of Mixed Pathology

For cerebrovascular disease (both are required)

- Documented history of stroke, or focal neurological features, or both
- MRI evidence of one or more of the followings: corresponding vascular lesions, small vessel disease, strategic lacunar infarcts, or cerebral haemorrhages

For Lewy body disease (both are required)

- One of the followings: extrapyramidal signs, early hallucinations, or cognitive fluctuations
- Abnormal dopamine transporter PET scan

2.3.4 DSM-5 Criteria for Mild or Major Neurocognitive Disorder due to AD 2013 [2.3b]

Major or Mild Neurocognitive Disorder due to Alzheimer's Disease

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).

C. Criteria are met for either probable or possible Alzheimer's disease as follows:

For major neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if either of the followings is present; otherwise, **possible Alzheimer's disease** should be diagnosed.

1. Evidence if a causative Alzheimer's disease genetic mutation from family history or genetic testing.
2. All three of the followings are present:
   a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).
   b. Steadily progressive, gradual decline in cognition, without extended plateaus.
   c. No evidence of mixed etiology (i.e. absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

For mild neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history.

Possible Alzheimer's disease is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the followings are present:

1. Clear evidence of decline in memory and learning.
2. Steadily progressive, gradual decline in cognition, without extended plateaus.

3. No evidence of mixed etiology (i.e. absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

2.3.5 NIA-AA Criteria for Dementia due to AD 2011 [2.3c] [2.3d]

NIA-AA Criteria for Probable AD Dementia

1. Meet criteria for dementia by NIA-AA
2. Insidious onset
3. Clear-cut history of worsening of cognition by report or observation
4. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
   a. Amnestic presentation
   b. Non-amnestic presentations:
      - Language presentation
      - Visuospatial presentation
      - Executive dysfunction
5. The diagnosis of probable AD dementia should not be applied when there is evidence of:
   a. Substantial concomitant cerebrovascular disease
   b. Core features of dementia with Lewy bodies
   c. Prominent features of behavioral variant frontotemporal dementia
   d. Prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia
   e. Another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition

Note : All patients who met criteria for “probable AD” by 1984 NINCDS-ADRDA criteria would meet the NIA-AA criteria for probable AD.

NIA-AA Criteria for Possible AD Dementia

Meets the core clinical criteria for AD dementia, but either of:

1. Atypical course
   - A sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline.
2. Etiologically mixed presentation
   - Concomitant cerebrovascular disease; or
   - Features of dementia with Lewy bodies; or
   - Evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition

Note : A diagnosis of "possible AD" by 1984 NINCDS-ADRDA criteria would not necessarily meet the NIA-AA criteria for possible AD dementia.

Dementia Unlikely to Be due to AD

1. Does not meet criteria for AD dementia.
2. a. Regardless of meeting clinical criteria for probable or possible AD dementia, there is sufficient evidence for an alternative diagnosis.
   b. Regardless of meeting clinical criteria for possible AD dementia, both amyloid beta (Aβ) and neuronal injury biomarkers are negative.

NIA-AA AD Dementia Criteria Incorporating Biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aß (PET or CSF)	Neuronal injury (CSF tau, FDG PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

2.3.6 NIA-AA Criteria for MCI due to AD 2011 [2.3e]

1. Cognitive concern reflecting a change in cognition reported by patient or informant or clinician.
2. Objective evidence of impairment in one or more cognitive domains, typically including memory.
3. Preservation of independent in functional abilities.
4. Not demented.
5. Etiology of MCI consistent with AD pathophysiological process:
   - Rule out vascular, traumatic, medical causes of cognitive decline, where possible.
   - Provide evidence of longitudinal decline in cognition, when feasible.
   - Report history consistent with AD genetic factors, where relevant.

MCI Criteria Incorporating Biomarker

Diagnostic category	Biomarker probability of AD etiology	Aß (PET or CSF)	Neuronal injury (CSF tau, FDG PET, structural MRI)
MCI - core clinical criteria	Uninformative	Conflicting/ indeterminant/ untested	Conflicting/ indeterminant/ untested
MCI due to AD - intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD - high likelihood	Highest	Positive	Positive
MCI - unlikely due to AD	Lowest	Negative	Negative

2.3.7 NIA-AA Preclinical Stage of AD 2011 [2.3f]

NIA-AA Criteria for Probable AD Dementia

1. It is intended for research purpose and has no clinical utility.
2. It bases on the concept that AD pathophysiological process (AD-P) emerges long before the clinical phase of AD, and thus AD is regarded as a continuum from preclinical stages to MCI, and to dementia.
3. There is no clinical diagnostic criterion for this stage.
4. It rests on the laboratory evidence of AD-P in an asymptomatic individual.
5. Laboratory tests involving Alzheimer's biomarkers are paramount for the detection of this stage.
6. Two major categories of Alzheimer's biomarkers:
   a. Biomarkers of Aß accumulation
      - Which are reductions in CSF $Aß_{42}$ and increased amyloid tracer retention on PET.
      - Is regarded as an initial event in AD-P.

   b. Biomarkers of neuronal degeneration or injury
      - Which are elevated CSF tau (both T-tau and P-tau); decreased FDG uptake on PET with temporoparietal pattern of hypometabolism; atrophy on structural MRI in a characteristic pattern involving the medial, basal, and lateral temporal lobes, and medial and lateral parietal cortices.
      - Presence of these biomarkers in addition to biomarkers of Aß accumulation may increase the likelihood of clinical decline to MCI within several years.
7. It is postulated that evidence of subtle cognitive decline detected by more sensitive cognitive measures, together with biomarkers evidence of Aß accumulation and neuronal injury, indicate the last stage of preclinical AD and are approaching MCI.

8. Proposed staging framework for preclinical AD:

Stage 1. Asymptomatic cerebral amyloidosis

- High PET amyloid tracer retention
- Low CSF $A\beta_{42}$

Stage 2. Amyloidosis + neurodegeneration

- Neuronal dysfunction on FDG PET/functional MRI
- High CSF T-tau/P-tau
- Cortical thinning/hippocampal atrophy in structural MRI

Stage 3. Amyloidosis + neurodegeneration + subtle cognitive decline

- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for mild cognitive impairment

2.3.8 Practical Notes on Alzheimer's Disease and Dementia [2.3g] [2.3h] [2.3i] [2.3j]

Making the Diagnosis of Dementia due to AD

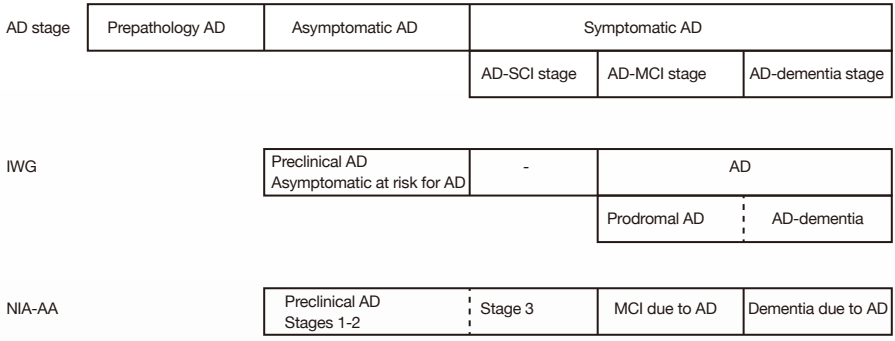
In the past, AD dementia syndrome is a clinical diagnosis by exclusion of some potential causes. There is no single reliable diagnostic investigation or imaging to rule in the disease. It relies on the history from patients and caregivers to establish the diagnosis. Therefore, it is always advisable to take history from reliable caregivers. It is not recommended to assess the patient in acute settings with presence of confounding medical and environmental factors.

IWG and NIA-AA criteria have transformed AD dementia diagnosis from a clinical diagnosis to a clinicobiological entity. In 2018, NIA-AA established a research framework towards a biomarker-based biological definition of AD in living people. It is not clinical diagnostic criteria or clinical guidelines and is intended for research purpose when this manual is published. However, the detection of the presence of AD pathology may become mandatory when disease modifying therapies become available and widely used in clinical settings. The definition and diagnostic criteria of AD will evolve accordingly. Please refer to Section 4.2: AD Biomarkers for details.

Alzheimer's Disease vs. Alzheimer's Dementia and IWG and NIA-AA Criteria

It is worthwhile to note that a number of elderly people suffer from Alzheimer's disease but not Alzheimer's dementia yet. The latter signifies that the patient has to exhibit features of dementia while the former signifies presence of Alzheimer's pathology e.g. amyloid plaques or tau proteins in the brain only. Early AD may be picked up by the advances in technology, e.g. the ratio of biomarkers such as low $A\beta_{42}$ and high P-tau level in the cerebrospinal fluid, or new neuroimaging techniques. This may allow detection of preclinical stage of AD, in the hope to prevent patients from evolving into the stage of clinical Alzheimer's dementia by earlier treatment. NIA-AA has developed criteria based on this conceptual framework about the pathophysiological evolution of AD. It encompasses preclinical stages of AD (solely for research purpose), MCI due to AD and finally AD dementia.

Both IWG and NIA-AA criteria provide a more detailed description of AD as a continuum of presentations, i.e. asymptomatic/pre-symptomatic and symptomatic stages. Yet they differ from each other as below:



Cognitive criteria

IWG criteria depict either impairment in episodic memory test, preferably one having encoding specificity (typical AD), or impairment in other non-memory domains forming a well-defined syndrome (atypical AD). NIA-AA criteria depict impairment in multiple cognitive domains and interference in activities of daily living (Note: Memory is not an absolute domain).

Biomarkers criteria

Biomarkers are parameters that can be measured in the body to reliably indicate the pathophysiological process of a disease. Biomarkers of AD are incorporated into both IWG and NIA-AA criteria. They are divided into two categories: (1) the biomarkers of Aß accumulation, which are PET evidence of Aß deposition and low CSF $Aß_{42}$, and (2) the biomarkers of neuronal degeneration or injury, which are elevated CSF tau (both T-tau and P-tau), decreased FDG uptake on PET in temporoparietal cortex; and disproportionate atrophy on structural MRI in medial, basal, and lateral temporal lobe, and medial and lateral parietal cortices. Integration of biomarkers into these guidelines is mainly for research purpose, in which the use of biomarkers is paramount in the detection of preclinical AD, whereas, it is complimentary in the diagnosis of MCI and dementia due to AD, as they are based primarily on clinical ground.

Both IWG and NIA-AA criteria have included biomarkers in the AD diagnosis, which is briefly summarized as below:

IWG and NIA-AA Criteria for AD-MCI and AD-dementia

Criteria	IWG	NIA-AA		
Cognitive criteria				
AD-MCI	Memory impairment	MCI		
AD-dementia	Memory impairment	Dementia		
Biomarker criteria			Amyloid marker	Injury marker
AD-MCI	Any amyloid or injury marker	High likelihood	+	+
AD-dementia		Intermediate likelihood	+	?
			?	+
		Uninformative	+	–
			–	+

+ = abnormal; – = normal; ? = not tested.

IWG uses either pathophysiological (amyloid, tau) or topographical (other) marker without further distinction.
NIA-AA criteria further divides into 3 stages:
Stage 1. amyloid marker alone;
Stage 2. amyloid + neuronal injury markers
Stage 3. amyloid + neuronal injury markers and symptomatic

DSM-5 vs. IWG and NIA-AA Criteria in AD

Both DSM-5 and NIA-AA criteria incorporate quantifiable cognitive test as an integral part of the diagnosis. NIA-AA does not specifically demand a reference value but DSM-5 differentiates mild and major NCD by different cut-offs. IWG and NIA-AA criteria start with meeting the criteria for dementia while DSM-5 starts with meeting the criteria for major or mild NCD. Both contain probable and possible AD. IWG and NIA-AA criteria contain the preclinical stage of AD which incorporates biomarkers for research application, whereas DSM-5 does not cover the preclinical stage of AD. MCI due to AD in NIA-AA is equivalent to DSM-5 mild NCD due to AD.

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2.4 Vascular Cognitive Disorders (VCD) and Vascular Cognitive Impairment (VCI)

2.4.1 Diagnostic Criteria for Vascular Cognitive Disorders – A VASCOG Statement 2014 [2.4a]

Evidence for Predominantly Vascular Etiology of Cognitive Impairment

(A) *One of the following clinical features*

(1) The onset of the cognitive deficits is temporally related to ≥1 cerebrovascular events (CVEs). (Onset is often abrupt with a stepwise or fluctuating course owing to multiple such events, with cognitive deficits persisting beyond 3 months after the event. However, subcortical ischemic pathology may produce a picture of gradual onset and slowly progressive course, in which case A2 applies.) The evidence of CVEs is one of the followings

(a) Documented history of a stroke, with cognitive decline temporally associated with the event

(b) Physical signs consistent with stroke (e.g. hemiparesis, lower facial weakness, Babinski sign, sensory deficit including visual field defect, pseudobulbar syndrome—supranuclear weakness of muscles of face, tongue and pharynx, spastic dysarthria, swallowing difficulties, and emotional incontinence)

(2) Evidence for decline is prominent in speed of information processing, complex attention, and/or frontal-executive functioning in the absence of history of a stroke or transient ischemic attack. One of the following features is additionally present

(a) Early presence of a gait disturbance (small-step gait or *marche petits* pas, or magnetic, apraxic-ataxic, or Parkinsonian gait); this may also manifest as unsteadiness and frequent, unprovoked falls

(b) Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease

(c) Personality and mood changes: abulia, depression, or emotional incontinence

(B) Presence of significant neuroimaging (MRI or CT) evidence of cerebrovascular disease (one of the followings)

(1) One large vessel infarct is sufficient for Mild VCD, and ≥2 large vessel infarcts are generally necessary for VaD (or Major VCD)

(2) An extensive or strategically placed single infarct, typically in the thalamus or basal ganglia may be sufficient for VaD (or Major VCD)

(3) Multiple lacunar infarcts (>2) outside the brainstem; 1-2 lacunes may be sufficient if strategically placed or in combination with extensive white matter lesions

(4) Extensive and confluent white matter lesions

(5) Strategically placed intracerebral hemorrhage, or ≥2 intracerebral hemorrhages

(6) Combination of the above

Exclusion criteria (for Mild and Major VCD)

(1) History

(a) Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia) in the absence of corresponding focal lesions on brain imaging or history of vascular events.

(b) Early and prominent Parkinsonian features suggestive of Lewy body disease

(c) History strongly suggestive of another primary neurological disorder such as multiple sclerosis, encephalitis, toxic or metabolic disorder, etc. sufficient to explain the cognitive impairment.

(2) Neuroimaging

(a) Absent or minimal cerebrovascular lesions on CT or MRI

(3) Other medical disorders severe enough to account for memory and related symptoms

(a) Other disease of sufficient severity to cause cognitive impairment, e.g. brain tumor, multiple sclerosis, encephalitis

(b) Major depression, with a temporal association between cognitive impairment and the likely onset of depression

(c) Toxic and metabolic abnormalities, all of which may require specific investigations

(4) [For research: The presence of biomarkers for Alzheimer's disease (cerebrospinal Aβ and P-tau levels or amyloid imaging at accepted thresholds) exclude diagnosis of probable VCD, and indicate AD with CVD]

Criteria for Vascular Cognitive Disorder: Miscellaneous Aspects

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Level of certainty

(1) *Probable*

(a) Clinical criteria for VCD are supported by neuroimaging.

(b) Both clinical and genetic [e.g. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL; cerebral autosomal recessive arteriopathy with subcortical autosomal recessive leukoencephalopathy, CARASIL; hereditary endotheliopathy retinopathy nephropathy and stroke, HERNS; pontine autosomal dominant microangiopathy and leukoencephalopathy, PADMAL; retinal vasculopathy with cerebral leukodystrophy, RVCL; collagen type IV, α1 (COL4A1)-related disorders] evidence of cerebrovascular disease

[For research: The presence of biomarkers for Alzheimer's disease (cerebrospinal Aβ and P-tau levels or amyloid imaging at accepted thresholds) excludes the diagnosis of probable VCD]

(2) *Possible*

Clinical criteria for VCD are met, but neuroimaging is not available (if appropriate neuroimaging is available and not supportive of VCD, the diagnosis of possible VCD should not be made)

Subtypes of VCD

(I) Hemorrhagic or ischemic

(II) Cortical-subcortical or subcortical ischemic

Multiple causation

(1) VCD with concomitant AD (Major or Mild)

(a) Meets criteria for VCD (except for exclusion criteria)

(b) Meets criteria for AD (possible)

State which etiology is clinically more salient: vascular or Alzheimer's

(2) VCD with additional pathology: e.g. Lewy body disease

(3) VCD with contribution from depression

Associated behavioral or psychiatric symptoms: with psychotic symptoms, depression, agitation, apathy, etc.

2.4.2 DSM-5 Criteria for Mild or Major Vascular Neurocognitive Disorder 2013 [2.4b]

Major or Mild Vascular Neurocognitive Disorder

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. The clinical features are consistent with a vascular etiology, suggested by either of the followings:
   1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.
   2. Evidence of decline is prominent in complex attention (including processing speed) and frontal-executive function.

C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.

D. The symptoms are not better explained by another brain disease or systemic disorder.

Probable vascular neurocognitive disorder is diagnosed if one of the followings is present; otherwise **possible vascular neurocognitive disorder** should be diagnosed:

1. Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported).
2. The neurocognitive syndrome is temporally related to one or more documented cerebrovascular events.
3. Both clinical and genetic (e.g. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present.

Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.

2.4.3 AHA-ASA Criteria for Vascular Cognitive Impairment 2011 [2.4c]

Diagnostic Criteria for Vascular Cognitive Impairment

1. The term vascular cognitive impairment (VCI) characterizes all forms of cognitive deficits from vascular dementia (VaD) to mild cognitive impairment (MCI) of vascular origin.
2. These criteria cannot be used for subjects who have an active diagnosis of drug or alcohol abuse/dependence. Subjects must be free of any type of substance for at least 3 months.
3. These criteria cannot be used for subjects with delirium.

Probable VaD

1. Meet criteria for dementia
   - It should be based on a decline in cognitive function from a prior baseline and a deficit in performance in ≥2 cogntive domains that are of sufficient severity to affect the subject's activities of daily living.
   - It must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions.
   - The deficits in activities of daily living are independent of the motor/sensory sequelae of the vascular event.
2. There is cognitive impairment and imaging evidence of cerebrovascular disease and
   - There is a clear temporal relationship between a vascular event and the onset of cognitive deficits, or
   - There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology.
3. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a non-vascular neurodegenerative disorder.

Possible VaD

1. Meet criteria for dementia
2. There is cognitive impairment and imaging evidence of cerebrovascular disease but
   - There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease and onset of cognitive impairment.
   - There is insufficient information for the diagnosis of VaD (e.g. clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
   - Severity of aphasia precludes proper cognitive assessment.
   - There is evidence of other neurodegenerative disease or conditions in addition to cerebrovascular disease that may affect cognition.

2.4.4 AHA-ASA Criteria for Vascular MCI 2011 [2.4c]

1. Vascular MCI (VaMCI) includes the 4 subtypes proposed for the classification of MCI: amnestic, amnestic plus other domains, non-amnestic single domain, and non-amnestic multiple domain.
2. The classification of VaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least 1 cognitive domain.
3. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms.

Probable VaMCI

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and
   - There is a clear temporal relationship between a vascular event and onset of cognitive deficits, or
   - There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortial cerebrovascular disease pathology.
2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a non-vascular neurodegenerative disorder.

Possible VaMCI

There is cognitive impairment and imaging evidence of cerebrovascular disease but

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease and onset of cognitive deficits.
2. There is insufficient information for the diagnosis of VaMCI (e.g. clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
3. Severity of aphasia precludes proper cognitive assessment.
4. There is evidence of other neurodegenerative disease or conditions in addition to cerebrovascular disease that may affect cognition.

2.4.5 Practical Notes on Vascular Cognitive Disorders (VCD) and Vascular Cognitive Impairment (VCI)

VCD (VASCOG)/VCI (AHA-ASA) refers to cognitive disorder associated with cerebrovascular diseases (e.g. frank stroke, vascular brain injury or subclinical vascular disease), regardless of the underlying pathogenesis (e.g. cardioembolic, atherosclerotic, ischemic, hemorrhagic, or genetic).

VCD/VCI should become a more preferred term, because:

- Similar as AD, VCD/VCI lies on a continuum from vascular MCI to vascular dementia.
- Potentially disease-modifying treatment may be available and more effective at MCI stage before approaching dementia stage.

More evidence shows that, unlike typical AD dementia, memory impairment is not a prerequisite feature for VCD/VCI; rather preponderance of disturbance in VCD/VCI is in processing speed and frontal-executive functions, manifesting as slowed information processing, impaired working memory and reduced set-shifting ability.

VCD/VCI vs. AD

- VCD/VCI can co-exist with multiple cerebral and systemic disorders that can affect cognition in the elderly, especially AD. Therefore, it is often difficult to determine whether the cognitive deterioration is solely a consequence of vascular factors or underlying AD.
- Perhaps even more complex is that AD can follow a stroke, or patients with AD symptomatology can have strokes during the course of the disease.
- Subtle and complicated relationship between either macroscopic or microscopic infarcts and AD exists.

Distinguishing

- VCD/VCI tends to affect memory domain lately; typical AD tends to affect memory domain early.
- VCD/VCI currently does not have any accepted confirmatory neuropathological criteria (since determining the volume or number of macroscopic infarcts necessary for VCD/VCI has been proved difficult); AD has an evolving clinicobiological (biomarker) criteria.

Overlapping

- Vascular lesions can lower the threshold for the clinical manifestation of AD.
- Hippocampal atrophy, a neurodegenerative marker for AD, may also be caused by vascular disease.
- Pathological and clinical evidence for cholinergic compromise in both VCD/VCI and AD, and thus cholinesterase inhibitors have been tested for both disorders in clinical trials.

2.4.6 Practical Notes on Mixed Dementia

Sometimes it would be difficult to differentiate whether the dementia is caused by neurodegeneration or cerebrovascular disease. A diagnosis of mixed dementia is often made at this juncture. Mostly it is an overlap between AD and VCD. Currently there are no specific established criteria.

It can be defined as cognitive decline sufficient to impair independent functioning in daily life resulting from the co-occurrence of AD brain pathology and cerebrovascular brain pathology, documented either by clinical criteria or neuroimaging findings.

It is most commonly found in the elderly as both neurodegeneration and cerebrovascular disease often co-exist in this population.

References

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2.5 Frontotemporal Dementia (FTD)

2.5.1 DSM-5 Criteria for Frontotemporal Neurocognitive Disorder 2013 [2.5a]

Major or Mild Frontotemporal Neurocognitive Disorder

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. The disturbance has insidious onset and gradual progression.

C. Either (1) or (2):
   1. Behavioral variant:
      a. Three or more of the following behavioral symptoms:
         i. Behavioral disinhibition.
         ii. Apathy or inertia.
         iii. Loss of sympathy or empathy.
         iv. Perseverative, stereotyped or compulsive/ritualistic behavior.
         v. Hyperorality and dietary changes.
      b. Prominent decline in social cognition and/or executive abilities.
   2. Language variant:
      a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension.

D. Relative sparing of learning and memory and perceptual-motor function.

E. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Probable frontotemporal neurocognitive disorder is diagnosed if either of the followings is present; otherwise, **possible frontotemporal neurocognitive distorder** should be diagnosed:

1. Evidence of a causative frontotemporal neurocognitive disorder genetic mutation, from either family history or genetic testing.
2. Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging.

Possible frontotemporal neurocognitive disorder is diagnosed if there is no evidence of a genetic mutation, and neuroimaging has not been performed.

2.5.2 International Consensus Criteria for Behavioral Variant FTD (bvFTD) 2011 [2.5b]

I. Neurodegenerative Disease

The following symptom must be present to meet criteria for behavioral variant FTD (bvFTD)

A. Shows progressive deterioration of behavior and/or cognition by observation or history

II. Possible bvFTD

Three of the following behavioral/cognitive symptoms (A-F) must be present to meet criteria.

A. Early (first 3 years) behavioral disinhibition (one of the following symptoms must be present) :
   A.1. Socially inappropriate behavior
   A.2. Loss of manners or decorum
   A.3. Impulsive, rash or careless actions

B. Early (first 3 years) apathy or inertia (one of the following symptoms must be present) :
   B.1. Apathy
   B.2. Inertia

C. Early (first 3 years) loss of sympathy or empathy (one of the following symptoms must be present) :
   C.1. Diminished response to other people's needs and feelings
   C.2. Diminished social interest, interrelatedness or personal warmth

D. Early (first 3 years) perseverative, stereotyped or compulsive/ritualistic behavior (one of the following symptoms must be present) :
   D.1. Simple repetitive movements
   D.2. Complex, compulsive or ritualistic behaviors

E. Hyperorality and dietary changes (one of the following symptoms must be present):
   E.1. Altered food preferences
   E.2. Binge eating, increased consumption of alcohol or cigarettes
   E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following symptoms must be present) :
   F.1. Deficits in executive tasks
   F.2. Relative sparing of episodic memory
   F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms must be present to meet criteria

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

C. Imaging results consistent with bvFTD (one of the followings must be present):
   C.1. Frontal and/or anterior temporal atrophy on MRI or CT
   C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. bvFTD with definite frontotemporal lobar degeneration (FTLD) pathology

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD

B. Histopathological evidence of FTLD on biopsy or at post-mortem

C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders

B. Behavioral disturbance is better accounted for by a psychiatric diagnosis

C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

2.5.3 International Consensus Criteria – Classification of Primary Progressive Aphasia (PPA) and its Variants 2011 [2.5c] [2.5d]

Inclusion and Exclusion Criteria for the Diagnosis of PPA: Based on Criteria by Mesulam

Inclusion: criteria 1-3 must be answered positively
1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease
Exclusion: criteria 1-4 must be answered negatively for a PPA diagnosis
1. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments
4. Prominent, initial behavioral disturbance

Diagnostic Features for the Non-Fluent Agrammatic Variant PPA, Semantic Variant PPA and Logopenic Variant PPA

Diagnostic Features	Non-Fluent Agrammatic Variant PPA	Semantic Variant PPA	Logopenic Variant PPA
Clinical diagnosis	Core features (at least 1): 1. Agrammatism in language production 2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech) Other features (at least 2 of 3): 1. Impaired comprehension of syntactically complex sentences 2. Spared single-word comprehension 3. Spared object knowledge	Core features (both): 1. Impaired confrontation naming 2. Impaired single-word comprehension Other features (at least 3): 1. Impaired object knowledge, particularly for low-frequency or low-familiarity items 2. Surface dyslexia or dysgraphia 3. Spared repetition 4. Spared speech production (grammar and motor speech)	Core features (both): 1. Impaired single-word retrieval in spontaneous speech and naming 2. Impaired repetition of sentences and phrases Other features (at least 3): 1. Speech (phonologic) errors in spontaneous speech and naming 2. Spared single-word comprehension and object knowledge 3. Spared motor speech 4. Absence of frank agrammatism
Imaging supported diagnosis	Both criteria: 1. Clinical diagnosis above 2. Imaging (one or more): a. Predominant left posterior fronto-insular atrophy on MRI b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET	Both criteria: 1. Clinical diagnosis above 2. Imaging (one or more): a. Predominant anterior temporal lobe atrophy b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET	Both criteria: 1. Clinical diagnosis above 2. Imaging (at least 1): a. Predominant left posterior perisylvian or parietal atrophy on MRI b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET
Diagnosis with definite pathology	Clinical diagnosis (criterion 1) and either criterion 2 or 3: 1. Clinical diagnosis above 2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other) 3. Presence of a known pathogenic mutation	Clinical diagnosis (criterion 1) and either criterion 2 or 3: 1. Clinical diagnosis above 2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other) 3. Presence of a known pathogenic mutation	Clinical diagnosis (criterion 1) and either criterion 2 or 3: 1. Clinical diagnosis above 2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. AD, FTLD-tau, FTLD-TDP, other) 3. Presence of a known pathogenic mutation

2.5.4 Practical Notes on FTD

Two broad presentations of FTD are recognized: bvFTD and PPA.

The 1998 consensus criteria by Neary and colleagues are the most widely adopted diagnostic guideline for FTD. After years of knowledge accumulation, a revised guideline for bvFTD and a new classification system for PPA and its three main clinical variants, were published in 2011.

Revised Diagnostic Criteria for bvFTD 2011

The revised guideline for bvFTD was developed by the International Behavioral Variant FTD Criteria Consortium. It simplified the 1998 criteria and focused on features that best distinguish bvFTD from psychiatric disorders, AD and other dementing conditions. Hence, it does not need to distinguish between core and supportive features, and does not need to take account of a number of restrictive exclusion features. These improve the sensitivity of the new criteria compared with the 1998 criteria. Another advance in the new criteria is the diagnostic hierarchy in which distinction between possible, probable or definite bvFTD with FTLD pathology depends on the level of diagnostic certainty.

Classification of PPA and its Variants 2011

A classification system for PPA and its 3 main variants (non-fluent/agrammatic, semantic, and logopenic) was formulated by an international group of PPA investigators, with the objective of unifying the heterogeneous clinical criteria adopted across centers. With the new classification system, patients should first meet basic PPA criteria. Then, they are divided into clinical variants based on specific speech and language features. They can be further specified as “imaging-supported” if the expected pattern of atrophy is found and “with definite pathology” if pathologic or genetic data are available. It is worth noting that PPA has clinical and pathological overlap of FTLD spectrum of disorder and AD pathology. Furthermore, there is no direct correlation between PPA clinical phenotypes and pathologic or genetic findings.

Practical Guide on Frontal Lobe Assessment [2.5e][2.5f]

1. History
   - Personality changes
   - Hyperorality
   - Distractibility
   - Poor motivation
   - Inability to adapt to new situations
   - Poor problem-solving skills

2. Frontal Release Reflexes
   - Grasp : Stroke patient's palm from radial to ulnar side. Patient will grasp your hand.
   - Pout : Stroke the filtrum or tap a spatula placed over lips. The lips will pout or make a contraction resembling a snout.
   - Palmomental : Stroke patient's thenar eminence and the patient's mentalis muscle will contract.

3. Simple Bedside Tests

Abstract thinking	: Proverb interpretation "People in glass houses should not throw stones at others" Similarities test "What are the similarities between apple and banana/table and chair?"
Cognitive estimates	: "What is the height of an average woman?" "What is now the population of Hong Kong?"
Verbal fluency	: "Tell me the names of as many animals as you can think of, as quickly as possible."
Luria's three-step test (Motor sequencing)	: Tell the patient that you are going to show them a series of hand movements. Demonstrate fist, edge and palm five times on your leg without verbal prompts. Ask the patient to repeat the sequence.

Go no go test	: Ask the patient to make a response to one signal (Go) and not to respond to another signal (No go). The most basic is to ask the patient to tap their knee when examiner says, “Go” and to make no response when the examiner says, “Stop”.
Stroop Test	: Ask the patient to state the color in which words are printed rather than words themselves, e.g. “RED” may be printed in blue, the patient should say BLUE; “GREEN” may be printed in red, the patient should say RED.

Tips for Clinicians

1. It is not practical to do all the frontal lobe tests during the busy clinic time. The above bedside tests may serve to immediately test the suspicion generated during history taking.
2. MMSE, while commonly used, is an insensitive tool for screening frontal lobe dysfunction.
3. MoCA includes several tasks sensitive to frontal lobe dysfunction:
   - mini trail-making test for visuospatial/executive function
   - tests of attention
   - verbal fluency
   - similarities test for abstraction.

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2.6 Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD)

2.6.1 DLB Diagnostic Criteria 2017: Fourth Consensus Report of the DLB Consortium [2.6a]

Revised Criteria for the Clinical Diagnosis of Probable and Possible Dementia with Lewy Bodies (DLB)

Essential for a diagnosis of **DLB** is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core Clinical Features *(The first 3 typically occur early and may persist throughout the course.)*

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, which may precede cognitive decline.
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive Clinical Features

Severe sensitivity to anti-psychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g. constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative Biomarkers

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

Supportive Biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG PET imaging.

Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Probable DLB can be diagnosed if:

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or
b. Only one core clinical feature is present, but with one or more indicative biomarkers.

Probable DLB should not be diagnosed on the basis of biomarkers alone.

Possible DLB can be diagnosed if:

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or
b. One or more indicative biomarkers is present but there are no core clinical features.

DLB is less likely:

a. In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or
b. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

2.6.2 DSM-5 Criteria for Neurocognitive Disorder with Lewy Bodies 2013 [2.6b]

Major or Mild Neurocognitive Disorder with Lewy Bodies

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. The disorder has an insidious onset and gradual progression.

C. The disorder meets a combination of core diagnostic features and suggestive diagnostic features for either probable or possible neurocognitive disorder with Lewy bodies.

For probable major or mild neurocognitive disorder with Lewy bodies, the individual has two core features, or one suggestive feature with one or more core features.

For **possible major or mild neurocognitive disorder with Lewy bodies**, the individual has only one core feature, or one or more suggestive features.

1. Core diagnostic features:
   a. Fluctuating cognition with pronounced variations in attention and alertness.
   b. Recurrent visual hallucinations that are well formed and detailed.
   c. Spontaneous features of parkinsonism, with onset subsequent to the development of cognitive decline.
2. Suggestive diagnostic features:
   a. Meet scriteria for rapid eye movement sleep behavior disorder.
   b. Severe neuroleptic sensitivity.

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

2.6.3 DSM-5 Criteria for Neurocognitive Disorder due to Parkinson's Disease 2013 [2.6b]

Major or Mild Neurocognitive Disorder due to Parkinson's Disease

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder.

B. The disturbance occurs in the setting of established Parkinson's disease.

C. There is insidious onset and gradual progression of impairment.

D. The neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder.

Major or mild neurocognitive disorder probably due to Parkinson's disease should be diagnosed if 1 and 2 are both met. **Major or mild neurocognitive disorder possibly due to Parkinson's disease** should be diagnosed if 1 or 2 is met:

1. There is no evidence of mixed etiology (i.e. absence of other neurodegenerative or cerebrovascular disease or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).
2. The Parkinson's disease clearly precedes the onset of the neurocognitive disorder.

2.6.4 PDD Diagnostic Criteria 2007 [2.6c]

1. The Core Features Must Be Present:

- Prior diagnosis of Parkinson's disease
- A dementia syndrome causing a decline in function severe enough to impair the patient in daily activities

2. Associated Clinical Features:

- At least 2 cognitive domains:
  - Impaired attention - which may fluctuate over time
  - Impaired executive function - impairment in complex thought processes such as in initiating an action, planning, or organization
  - Impaired visuo-spatial ability - marked deficits in the processing of visual-spatial material
  - Impaired free recall memory - which improved with cueing
- At least one behavioral symptoms
  - Apathy - decreased spontaneity, motivation, effortful behavior
  - Changes in personality and mood - can include depression and anxiety
  - Hallucinations - usually complex and visual
  - Delusions - usually paranoid delusions, such as infidelity or perceived unknown guests in the home
  - Excessive daytime sleepiness

3. Features which do not exclude PDD, but make the diagnosis uncertain:

- Existence of an abnormality which causes cognitive impairment although not determined to cause dementia
- If the duration of time between the onset of motor and cognitive symptoms is not known

4. None of the following features present:

- Cognitive or behavioral symptoms which occur only in existing conditions, such as systemic diseases, drug intoxication, or major depression
- Symptoms compatible with vascular dementia

2.6.5 Practical Notes on DLB and PDD [2.6a] [2.6b] [2.6c] [2.6d]

Dementia with Lewy Bodies

Diagnostic criteria for DLB refined by the DLB Consortium in the Fourth Consensus Report in 2017 have been the most widely accepted diagnostic criteria for DLB. The dementia features are different from that of typical AD. Deficits of attention, executive function and visuoperceptual ability may be prominent in the early stages while memory impairment may not occur.

The patients have fluctuating cognition, attention or alertness over hours or days which is typically delirium-like. They have recurrent visual hallucinations with well-formed and detailed images of people or animals (up to 80%) (sometimes accompanied by related phenomena including passage hallucinations, sense of presence and visual illusions). Spontaneous parkinsonian features eventually occur in over 85%. REM sleep behavior disorder may precede cognitive decline.

Parkinson's Disease Dementia

About 18-40% of patients with Parkinson's disease have dementia. A diagnosis of Parkinson's disease must be made years before dementia was noted. In general, Parkinson's disease should exist at least 1 year prior to the onset of dementia (the 1-year rule).

Risk factors for developing dementia include more advanced Parkinson's disease, co-existing depression and the absence of prominent tremor.

DLB and PDD

DLB and PDD share many common pathological and clinical features. Whether they are different entities or part of the same Lewy body disease is still debatable.

In terms of neuropsychiatric profiles, DLB/PDD patients have more visuoperceptual, visuoconstructional and attentional deficits, while AD patients have more prominent memory impairment. Hence, MMSE may not be sensitive enough for screening DLB/PDD while MoCA has adequate psychometric properties and may serve as a more appropriate screening instrument. [2.6d]

The temporal sequence of symptoms is most crucial in the differentiation between DLB and PDD. DLB should be diagnosed when dementia occurs before, at the same time, shortly after the onset of parkinsonism. PDD should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule (arbitrary cut-off) between the onset of dementia and parkinsonism continues to be recommended.

Other helpful features include: DLB has faster clinical decline, decreased levodopa responsiveness, less prominent tremors and more cognitive fluctuation.

The DSM-5 criteria for NCD with Lewy bodies and NCD due to Parkinson's disease are in general in line with the expert panel criteria.

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2.7 Progressive Supranuclear Palsy (PSP)

2.7.1 PSP Diagnostic Criteria 2017 by Movement Disorder Society [2.7a]

Basic Features

B1: Mandatory inclusion criteria
1. Sporadic occurrence
2. Age 40 or older at onset of first PSP-related symptom
3. Gradual progression of PSP-related symptoms

B2, B3: Mandatory and context dependent exclusion criteria. Please refer to [2.7a] for details.

Core Clinical Features

	Functional Domain			
Levels of Certainty	Ocular Motor Dysfunction	Postural Instability	Akinesia	Cognitive Dysfunction
Level 1	O1: Vertical supranuclear gaze palsy	P1: Repeated unprovoked falls within 3 years	A1: Progressive gait freezing within 3 years	C1: Speech/language disorder, i.e. non-fluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	O2: Slow velocity of vertical saccades	P2: Tendency to fall on the pull-test within 3 years	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa-resistant	C2: Frontal cognitive/behavioral presentation
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: More than two steps backward on the pull-test within 3 years	A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	C3: Corticobasal syndrome

Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers.

Supportive Features

Clinical Clues	Imaging Findings
CC1: Levodopa-resistance	IF1: Predominant midbrain atrophy or hypometabolism
CC2: Hypokinetic, spastic dysarthria	IF2: Postsynaptic striatal dopaminergic degeneration
CC3: Dysphagia	
CC4: Photophobia	

Degrees of Diagnostic Certainty, Obtained by Combinations of Clinical Features and Clinical Clues

Diagnostic Certainty	Definition	Combinations	Predominance Type
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation
Probable PSP	Highly specific, but not very sensitive for PSP *Suitable for therapeutic and biological studies*	(O1 or O2) + (P1 or P2)	PSP with Richardson's syndrome
		(O1 or O2) + A1	PSP with progressive gait freezing
		(O1 or O2) + (A2 or A3)	PSP with predominant parkinsonism
		(O1 or O2) + C2	PSP with predominant frontal presentation
Possible PSP	Substantially more sensitive, but less specific for PSP *Suitable for descriptive epidemiological studies and clinical care*	O1	PSP with predominant ocular motor dysfunction
		O2 + P3	PSP with Richardson's syndrome
		A1	PSP with progressive gait freezing
		(O1 or O2) + C1	PSP with predominant speech/language disorder[a]
		(O1 or O2) + C3	PSP with predominant CBS[a]
Suggestive PSP	Suggestive of PSP, but not passing the threshold for possible or probable PSP *Suitable for early identification*	O2 or O3	PSP with predominant ocular motor dysfunction
		P1 or P2	PSP with predominant postural instability
		O3 + (P2 or P3)	PSP with Richardson's syndrome
		(A2 or A3) + (O3, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with predominant parkinsonism
		C1	PSP with predominant speech/language disorder
		C2 + (O3 or P3)	PSP with predominant frontal presentation
		C3	PSP with predominant CBS

The basic features B1+B2+B3 apply for all probable, possible and suggestive criteria. Core clinical features are defined by their functional domain (O, P, A and C) and stratified by presumed levels of certainty they contribute to the diagnosis of PSP. Supportive clinical clues (CC) are presented.
[a]Probable 4R-tauopathy (i.e. either PSP or CBD).

2.7.2 Practical Notes on PSP

PSP is characterized pathologically by intracerebral aggregation of the microtubule-associated protein tau, a definite diagnosis depends on neuropathological examination.

In the latest Movement Disorder Society Criteria of Progressive Supranuclear Palsy (MDS-PSP) published in 2017, there are four core domains to diagnose PSP clinically, namely (1) ocular motor dysfunction, (2) postural instability, (3) akinesia and (4) cognitive dysfunction. Each core domain has 3 levels of certainty according to clinical features. In addition, 7 supportive features about clinical clues and imaging findings are ancillary evidence to help the diagnosis. This criterion helps clinicians to diagnose early and variant PSP.

The variant PSP includes PSP with ocular motor dysfunction (PSP-OM), postural instability (PSP-PI), Parkinsonism resembling idiopathic Parkinson's disease (PSP-P), progressive gait freezing (PSP-PGF), frontal lobe cognitive or behavioral presentations (PSP-F), speech/language disorders (PSP-SL), corticobasal syndrome (PSP-CBS), primary lateral sclerosis (PSP-PLS) and cerebellar ataxia (PSP-C).

As many as 50% of patients with PSP presented with cognitive symptoms in the early stage of their disease.

Unlike patients with AD who have significant impairment in episodic memory, patients with PSP mainly have frontal lobe dysfunction, e.g. impaired abstract thinking, motor perseveration and frontal behavioral disturbances.

Patients with PSP typically have early executive dysfunction, e.g. difficulty in planning and organization, which can be assessed by simple bedside test such as verbal fluency.

Language deficits can mimic progressive non-fluent aphasia (PNFA), with agrammatism, apraxia of speech, or hesitant and effortful speech, which limit their verbal interaction.

Behavioral symptoms such as apathy, disinhibition, impulsivity, anxiety and depression are common. Insomnia or difficulties in maintaining sleep are frequently reported by patients with PSP.

Reference

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2.8 Corticobasal Degeneration (CBD)

2.8.1 Criteria for the Diagnosis of CBD 2013 [2.8a]

Proposed Clinical Phenotypes (Syndromes) Associated with the Pathology of Corticobasal Degeneration

Syndrome	Features
Probable corticobasal syndrome	Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
Non-fluent/agrammatic variant of primary progressive aphasia	Effortful, agrammatic speech plus at least one of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

2.8.2 Practical Notes on CBD

Pathologically confirmed CBD is characterized by tauopathy. There are different phenotypes associated with this CBD pathology. A systematic review published in 2013 identified five representative CBD phenotypes (namely probable and possible corticobasal syndrome (CBS), frontal behavioral-spatial syndrome, non-fluent/agrammatic variant of primary progressive aphasia and progressive supranuclear palsy syndrome) and established the diagnostic guidelines respectively. Two sets of diagnostic criteria for CBS were defined. One is more specific clinical research criteria for probable CBS. Another is broader criteria for possible CBS which are more inclusive but have a higher chance to detect other tau-based pathologies. [2.8a]

Cognitive decline is a common presenting and prominent feature of CBD. Systemic reviews showed that up to 70% of patients with CBD have cognitive impairment.[2.8a] Meanwhile, some CBD patients presented with cognitive symptoms may never develop motor features.

Apraxia is a core feature of cognitive impairment in patients with CBD.

Common types of apraxia described in patients with CBD:

- Ideomotor apraxia: inability to plan or act out motor actions that rely on semantic memory, e.g. fail to pretend to brush his teeth
- Limb-kinetic apraxia: inability for limbs to perform precise and voluntary movements, e.g. cannot wave hello by hand
- Apraxia of speech: difficult to plan and coordinate the movements for speech

Aphasia occurred in about half of the patients over the disease course, and it may progress to mutism.

Other cognitive features reported include executive dysfunction, behavioral changes and depression, while episodic memory is relatively preserved.

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2.9 Creutzfeldt-Jakob Disease (CJD)

2.9.1 CDC's Diagnostic Criteria for CJD 2018 [2.9a]

1. Sporadic CJD

Definite:

- Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and/or presence of scrapie-associated fibrils.

Probable:

- Neuropsychiatric disorder plus positive RT-QuIC in cerebrospinal fluid (CSF) or other tissues

OR

- Rapidly progressive dementia; and at least two out of the following four clinical features:
  1. Myoclonus
  2. Visual or cerebellar signs
  3. Pyramidal/extrapyramidal signs
  4. Akinetic mutism

AND a positive result on at least one of the following laboratory tests:

- A typical EEG (periodic sharp wave complexes) during an illness of any duration
- A positive 14-3-3 CSF assay in patients with a disease duration of less than 2 years
- High signal in caudate/putamen on magnetic resonance imaging (MRI) brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)

AND without routine investigations indicating an alternative diagnosis.

Possible:

- Progressive dementia; **and** at least two out of the following four clinical features:
  1. Myoclonus
  2. Visual or cerebellar signs
  3. Pyramidal/extrapyramidal signs
  4. Akinetic mutism

AND the absence of a positive result for any of the four tests above that would classify a case as "probable"
AND duration of illness less than two years
AND without routine investigations indicating an alternative diagnosis.

2. Iatrogenic CJD
• Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; or sporadic CJD with a recognized exposure risk, e.g. antecedent neurosurgery with dura mater implantation.

3. Familial CJD
• Definite or probable CJD **plus** definite or probable CJD in a first degree relative; and/or neuropsychiatric disorder **plus** disease-specific PrP gene mutation.

2.9.2 Practical Notes on CJD

The vast majority of CJD cases are sporadic (sCJD). Cognitive deficit is the first presenting symptoms in 40% of patients with sCJD. [2.9b] Memory loss is the most frequent, followed by aphasia and frontal/executive dysfunction. Common behavioral symptoms include agitation, irritability and depression.

There is rapid neuropsychiatric decline in patients with sCJD. With disease progression, dementia features become dominant and akinetic mutism may appear. Death usually occurs within one year of symptom onset.

A minority of patients have variant CJD (vCJD), which is the acquired form of this disease. The mean age of onset is younger (mean age of 29 years) than sCJD (mean age of 65 years). [2.9c] In addition, most patients with vCJD have more prominent psychiatric or behavioral symptoms on presentation, rather than neurological signs. Among these psychiatric symptoms, depression is most commonly reported, followed by apathy, anxiety, irritability, social withdrawal, agitation, and insomnia. Few patients have psychotic features, like delusions or hallucinations.

Traditionally, patients with rapidly progressive dementia are diagnosed to have probable sCJD if they have at least two out of the following four clinical features: myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs, and akinetic mutism; and a positive result in one of the following laboratory tests: a typical EEG feature, CSF assay for 14-3-3, high signal in caudate/putamen on MRI or at least two cortical regions either on DWI or FLAIR. With the development of a newer RT-QuIC (real-time quaking-induced conversion) essay,

probable sCJD can be diagnosed if patients with neuropsychiatric disorder are found positive for RT-QuIC in CSF or other tissues. RT-QuIC was first described in 2010. The technique can exploit the ability of the misfolded pathological form of prion protein to induce conversion of normal prion protein to the misfolded form, which subsequently aggregates and is monitored in real time using florescent dyes. This is the pathological hallmark feature seen in sCJD. The current sensitivity of CSF RT-QuIC undertaken at the UK National CJD Research and Surveillance Unit is 92% and the specificity is 100%. [2.9d]

References
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2.10 Delirium

2.10.1 DSM-5 Criteria for Delirium 2013 [2.10a]

- A disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).

- The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.

- An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).

- The disturbances in Criteria A and C are not better explained by another preexisting established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

- There is evidence from history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to medications), or exposure to a toxin, or is due to multiple etiologies.

Specify Cause:
- Substance intoxication delirium
- Substance withdrawal delirium
- Medication-induced delirium
- Delirium due to another medical condition
- Delirium due to multiple etiologies

Specify Onset and Duration:
- Acute: lasting a few hours or days
- Persistent: lasting weeks or months

Specify Type:
- Hyperactive
- Hypoactive
- Mixed level of activity

2.10.2 Confusion Assessment Method 1990 [2.10b]

The presence of features (1), (2) and either (3 or 4).

1. Acute onset and fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

2.10.3 4AT Cantonese 2019 [2.10c]

(1) 清醒度

包括明顯昏睡(例如:難以叫醒/明顯眼瞓)，以及激動/過度活躍的病人。觀察病人。如果病人瞓著，請用言語或者輕輕拍佢嘅膊頭去叫醒佢，可以請病人講出佢嘅名同埋地址去協助評分。

		✓
正常(評估時完全警覺而唔過分激動)	0	
醒後十秒有啲昏睡 之後正常	0	
明顯唔正常	4	

(2) 簡易認知測試 (AMT4)

(年齡) 你今年幾歲?
(出生日期) 你幾時生日?
(地點) 我地依家係乜嘢地方?
(年份) 今年係乜嘢年份?

全部答啱	0	
答錯一題	1	
答錯兩題或以上	2	

(3) 專注力

問病人:「請你用 30 減 3，然後再減 3，連續減 10 次。」(答案為 30，27，24，等)
*如有需要，可以俾提示「例如 30 減 3 係幾多呀? 」

能夠減啱 7 次或以上	0	
減啱少於 7 次/唔肯回答	1	
未能評估(因為唔舒服、太眼瞓、注意力唔集中)	2	

(4) 急性變化或波動

過去兩個星期開始有跡象晌清醒度，認知能力或其他精神狀態(例如:被迫害妄想，幻覺)上嘅明顯改變或波動。而晌過去嘅 24 小時內仍然可見。

冇	0	
有	4	

---

4 分或以上: 可能是譫妄和/或認知障礙
1 至 3 分: 可能是認知障礙
0 分: 不大可能是譫妄或嚴重認知障礙 (但譫妄仍可能存在如果第 4 項的資訊不完全)

指引：

4AT是為譫妄和認知障礙的快速初步評估而設計的篩查工具。 4 分或以上顯示譫妄但並非確診：確診可能需要對精神狀態更詳細的評估。1 至 3 分顯示認知障礙，需要更詳細的認知測試和知情者提供的病史。0 分不能絕對地排除譫妄或認知障礙：由臨床情況決定是否需要更詳細的測試。第一至三項完全由對病人評估時的觀察來評分。第四項需要一個或更多的資訊來源，例如：你自己對病人的認識，其他認識病人的員工（例如：病房護士），家庭醫生的轉介信，病案，照顧者。當進行測試或詮釋分數的時候，測試者需要考慮溝通上的困難（聽覺損害， 失語症，語言隔閡）。

清醒度：

在通常醫院的環境中，清醒度的轉變很大可能是譫妄。如果病人在臨床評估中顯示出清醒度的顯著轉變，這一項評四分。**AMT4（簡易認知測試-4）**：如剛剛做過 AMT10，這分數 可從 AMT10 中提取。**急性變化或波動**：在某些認知障礙症的病例中，波動性可以在沒有譫妄的情況下發生，但顯著的波動通常顯示是譫妄。如果想引得別人說出幻覺和/或妄想，問病人一些問題，例如，“你會不會對於這裡發生的任何事有關注？”“你會不會因任何事或人而感到驚恐？”“你有沒有看見或聽見任何奇怪的事情？”

2.10.4 Practical Notes on DSM-5 Criteria, CAM and 4AT for Delirium

Delirium is common in older adults with or without underlying dementia, and is an emergency condition.

In DSM-5, the exclusion of delirium is a prerequisite for the diagnosis of any form of NCD. DSM-5 has timely added in the clinically relevant etiological and descriptive specifiers to establish a comprehensive framework for the diagnosis of delirium. This can assist clinicians in the management of older delirious patients. Medication-induced delirium, delirium due to another medical condition and delirium due to multiple etiologies are common underlying causes of delirium in old age. It is worth noting that persistent delirium, on contrary to the conventional acute and short-lived delirium, can last for months. In reality, persistent delirium frequently occurs in older adults, yet this and the hypoactive form of delirium remain highly under-recognized in clinical practice. If the DSM-5 diagnostic criteria for delirium are being observed closely, these deficits hopefully can be alleviated in the future. [2.10a]

Despite the comprehensiveness of the DSM-5 delirium diagnostic criteria, the classical CAM items are still a practical guide in the detection of delirium for their inherent beauty of simplicity. [2.10b]

The 4AT is a simple, quick (<2 minutes) and effective bedside tool which helps practitioners to detect delirium in day-to-day practice. It does not require special training and is easy to implement and available in different translations including Cantonese. It is known to improve delirium detection rates in hospitals and other care settings. It has a large diagnostic test accuracy evidence base: a meta-analysis of 17 validation studies showed a pooled sensitivity of 88% and specificity of 88%. [2.10c]

References

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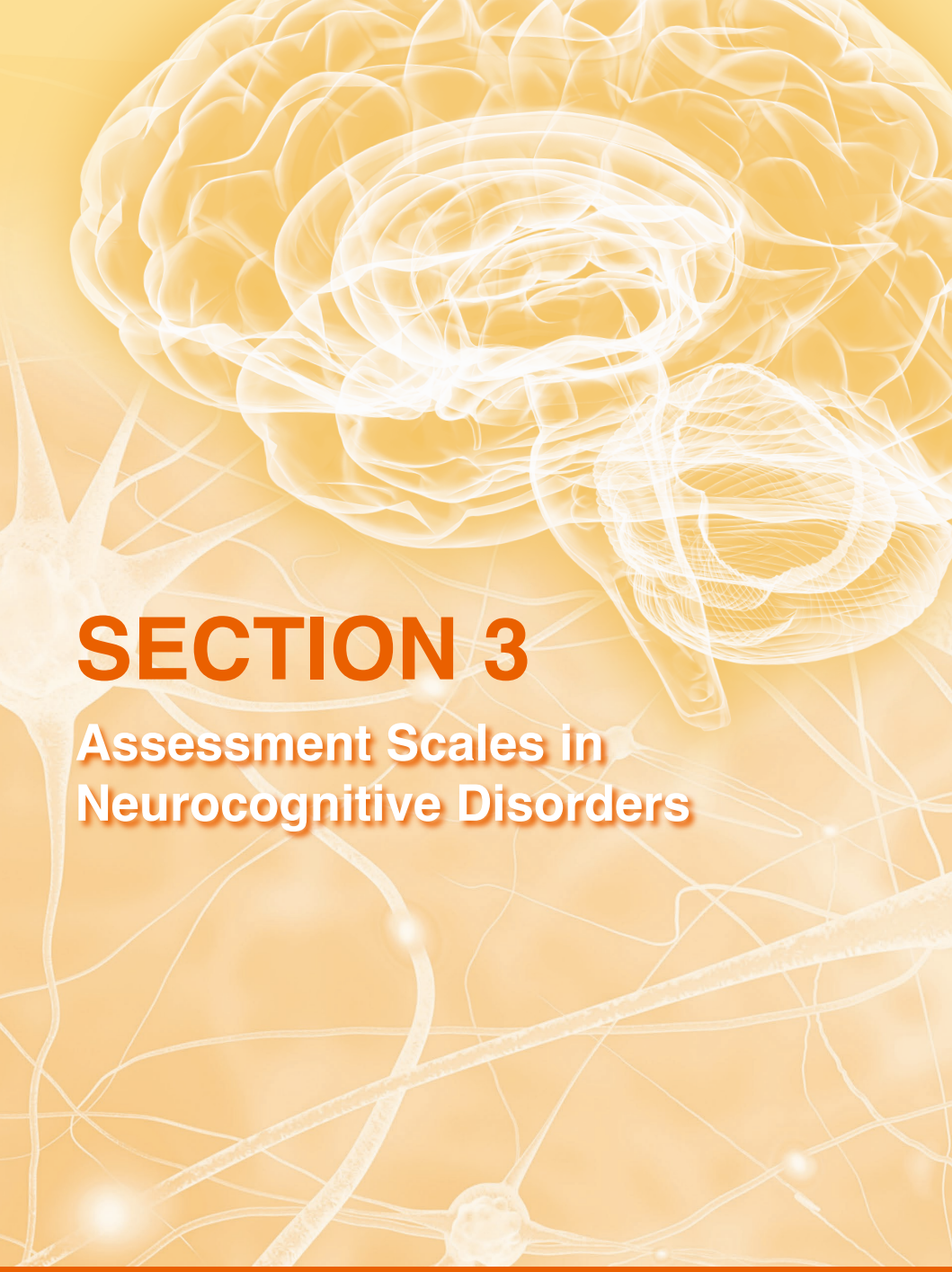


SECTION 3

Assessment Scales in Neurocognitive Disorders

SECTION 3

Assessment Scales in Neurocognitive Disorders

This section aims at providing a framework for commonly used assessment scales in neurocognitive disorders. As most of the scales are copyrighted, please refer to the website for the details for each individual scale.

3.1 Screening Tools for Dementia

3.1.1 Abbreviated Mental Test (AMT) [3.1a] [3.1b]

- 10 items scale.
- Takes ~3 minutes to administer.
- Assesses memory, orientation, registration and attention.
- It is a screening test, and not a test to monitor progress or drug response. Although a lower score is supposed to reflect lower cognitive function, the test was not designed for this purpose and hence should not be interpreted as such. It tells us whether the individual is "at risk" of cognitive impairment, but not its severity.
- Based on a local study involving 60 hospitalized older adults, [3.1a] a cutoff at 6 is suggested (below 6 is abnormal).
- A more recent study in Italy involving 2808 older adults found AMT >6 has a high negative predictive value (99%). AMT <7 has low positive predictive value (25%) meaning further test is needed to confirm dementia. [3.1b]

3.1.2 AD8 [3.1c] [3.1d]

- Takes ~3 minutes to administer.
- It is intended to administer to an informant, if informant is not available, it can be administered to the person to be screened.
- Consists of 8 questions to test for memory, orientation, judgement and function.
- Each question requires the responder to indicate: Yes, a change, or No, no change, or Don't know. The final score is the sum of the questions.
- Cut-off points are: 0-1: normal; 2 or above: cognitive impairment is likely.
- Scores in the impaired range indicate a need for further assessment. Scores in the "normal" range suggest that a dementing disorder is unlikely, but a very early disease process cannot be ruled out.
- Sensitivity >84%, specificity >80%, positive predictive value >85%, negative predictive value >70%. [3.1c]

- A Chinese version has been validated with good reliability (sensitivity 94%, specificity 76%). [3.1d]

3.1.3 Clock Drawing Test (CDT) [3.1e] [3.1f] [3.1g]

The Clock Drawing Test is a simple and popular screening tool for dementia. It takes two minutes and is a useful adjunct to the MMSE for a quick survey of global cognitive functions.

There are many variations but the usual instructions to the patient are to draw the clock face in a pre-drawn circle marking the hours and with the hands to indicate a particular time (e.g. 10 minutes past 11).

Practical Notes for CDT

1. Cognitive domains tested in CDT reflect frontal and temporo-parietal functioning, such as
   - Auditory comprehension
   - Language
   - Memory
   - Abstract thinking
   - Conceptualization of time
   - Visuo-spatial organization
   - Inhibition of distracting stimuli
   - Goal directed action planning
2. Scoring systems

   Numerous methods exist but none are proven superior in the screening for dementia, with similar sensitivity and specificity of around 86% and 87% respectively. The positive and negative predictive values ranged from 93-97% and 70-74% respectively, assuming a 20% clinic prevalence of dementia.

   For reference, a simple version and a local version are described briefly.

   - Simple method – Scoring system adopted from Mini-cog test (sensitivity 85%, specificity 86%).
     - 1 = correct if clock looks grossly normal with placement of correct time
     - 0 = incorrectly

- Hong Kong version as screening test in the elderly with low educational levels (sensitivity 83%, specificity 79%). It is a 2-part composite CDT with
  a. clock drawing scored with 0-10 points (Figure 2). Cut off points 3/4.
  b. reading and setting the time on a toy clock.

3. Qualitative interpretation
   - Simply observing the patient relays useful information to the physician.
   - Provides an educational impact on families.
   - Interpretation of common errors may assist understanding of the patient's cognitive deficits within the context of the presenting symptoms.

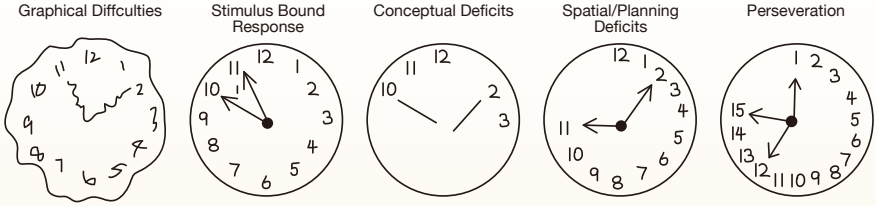
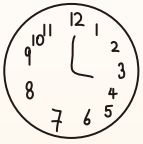


Figure 1. Representative illustration of common types of clock-drawing errors.

1. **Graphical errors** - hands and numbers imprecise and clumsy, but still appear recognizable as a clock. Impaired fine motor control and planning from disrupted frontostriatal circuits in, e.g. vascular dementia
2. **Stimulus-bound response errors** - drawing is dominated by a single stimulus, usually related to the time-setting instruction, e.g. instructed to "Set time to 11:10", patient fails to recode the '10 minutes' into setting the minute hand at "2".
3. **Conceptual deficits** - misrepresentations of the clock and time (e.g. does not look like a clock, hands do not communicate a time, hands are absent, time written on the clock). Impaired access to knowledge store of factual and conceptual knowledge, i.e. semantic memory of meaning/features of a clock, a function of lateral temporal lobes which is affected earlier in Alzheimer's disease (AD) than vascular dementia (VaD), Parkinson's disease dementia (PDD) or frontotemporal dementia (FTD).
4. **Spatial and/or planning deficits** - planning difficulties with irregular spacing between numbers, left hemi-neglect, numbers written outside clock-face or counter-clockwise direction. Impaired parietal lobe function, greater in PDD, DLB, VaD, AD than in FTD.
5. **Perseveration** - recurrence of activity without an appropriate stimulus, e.g. drawing more than 2 hands, repeating same numbers, or writing more beyond 12. These errors are common in AD and may be localized to the prefrontal area of the frontal lobe.

Instructions:
Fill inside a pre-drawn circle of 2.5" diameter the numbers of a clock with arms indicating the 3 o'clock position.

Scoring Criteria for Clock Drawing Test (CDT)

Score	Criteria	Example
0	Correct denotation of time with normal spacing	
1	Slight impairment in spacing of lines or numbers	
2	Noticeable impairment in line spacing	
3	Incorrect spacing between spokes (or numbers) with subsequent inappropriate denotation of time	
4	Obvious errors in correct time denotation (e.g. arms grossly misplaced, numbers drawn at wrong places)	
5	More obvious errors in time denotation (e.g. one arm omitted, circle the numbers or lines of clock face instead of drawing arms)	

6	Abnormal clock-face drawing with inaccurate time denotation (e.g. reversal of numbers, perseveration beyond twelve, misplaced numbers, drawing only to one side, omitting most numbers)	
7	A recognizable attempt to draw a clock face but with no clear denotation of time	
8	Some evidence that a clock face is drawn	
9	Minimal evidence that a clock face is drawn	
10	No reasonable or understandable attempt of drawing a clock face (excluding gross visual disturbance, hemiplegia, severe psychotic state, rendering uncooperativeness)	

Figure 2. Hong Kong CDT version.

3.1.4 Montreal Cognitive Assessment (MoCA)

- Takes ~10 minutes to administer.
- Assesses memory, language, attention, orientation, visuospatial and executive functions.
- MoCA tests frontal lobe functions e.g. inhibition, planning and language and thus will be useful in picking up frontotemporal dementia. However, for more specific assessment on frontal lobe function, Frontal Assessment Battery is suggested.
- It was originally designed for the screening of mild cognitive impairment (MCI)[3.1h] but now also has a cut-off for possible dementia in addition to possible MCI.
- It is a pencil-and-paper test and thus may be more difficult for those individuals with lower education. However, that also makes it a more appropriate test for those with higher education, eliminating the "ceiling effect" in the mini-mental state examination. It is always advisable to take a detailed history to compare the current with premorbid cognitive performances based on the patient's prior professional or scholastic attainment.
- The most widely used cut-off values in Hong Kong are derived from a local study done in 2015. This study suggested that the cut-off should be tailored according to age and education.[3.1i] It included 792 healthy subjects aged ≥ 65 years with MRI brain showed no significant brain pathology and medial temporal lobe atrophy. Norms of HK-MoCA scores were then described according to age and education level. The 2nd, 16th and 7th percentiles were described for the psychometric classification for major and mild neurocognitive disorder according to DSM-5 and MCI by Petersens' criteria respectively. It is also worthwhile to note that these cut-off values are purely based on population-based norms without physician's assessment. Subjects who score at below second percentile does not necessarily mean that they are having dementia.

- Please be reminded that there are different cut-off values validated locally. A local study [3.1j] suggested the cut off values for amnestic MCI at 22/23 (+1 for subjects with 6 years of education or less) yielding a sensitivity and specificity of 78% and 73%, while the cut off for dementia at 19/20 yielding a sensitivity and specificity of 94% and 92% respectively. Another local study [3.1k] suggested using a single cut-off at 21/22 (+1 for subjects with 6 years of education or less) to differentiate MCI from normal yielded a sensitivity of 86% and specificity of 72%. Whereas the sensitivity and specificity for identifying dementia using a cut-off at 18/19 were both 92%. The authors found that a large proportion of those who were diagnosed by clinicians as cognitively impaired would have been classified as normal if only age- and education-norm based cut-off were used. The largest discrepancies lied on those who are older (age >80 years) and received less education (0-6 years of education).
- Like any other tests, clinical judgement must be exercised for interpreting the result.
- MoCA 5-min has been validated in local stroke/TIA patients to screen for cognitive impairment.[3.1l] It tests memory, language fluency and orientation. It correlates well with the performance of MoCA and carries the benefit of being very brief and not requiring the participant to use a pen. The age- and education-based cut-off values for MoCA 5-min were also obtained from the previous local study.[3.1j] One Chinese study [3.1m] showed that MoCA 5-min did not differ from the MoCA in differentiating subacute stroke patients with cognitive impairments from those without, making MoCA 5-min a valid alternative screening tool for cognitive impairment in stroke patients.
- The down side of MoCA 5-min is that it has limited component to test for executive functions. It is not suitable to elicit deficit in frontal lobe function and visuospatial skills.
- Both HK-MoCA and HK-MoCA 5-min are available from CUHK website. [3.1n]

3.1.5 Hong Kong Brief Cognitive Test (HKBC) [3.1o]

- Takes ~7 minutes to administer.
- Assesses immediate recall/attention, delayed recall, recent memory, orientation, frontal lobe function test, general knowledge, visuospatial construction, executive function, and language.
- The background for the development of HKBC is that the performance on the MoCA is strongly influenced by education level. Also, there are at least 3 different sets of cut-off values for MoCA leading to uncertainty in interpreting the result.
- HKBC has the advantage of having only one single cutoff value. To differentiate normal from cognitively impaired (mild and major NCD), cut-off at ≤21 (no need to adjust for education) have a sensitivity 0.9, specificity 0.86, PPV 0.94 and NPV 0.99. With the same group of subjects, it was found that the cut-off for MoCA to differentiate normal from cognitively impaired is at ≤ 19. It reiterates the point that there is uncertain cut-off for MoCA.
- HKBC is suitable for screening cognitive impairment in local older adults with low educational level because it minimized use of paper and pencil test, modified the difficulty of clock-drawing, and naming of familiar objects.
- The form can be requested online via.[3.1p]

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3.2 Scales for Dementia Severity

3.2.1 Functional Assessment Staging (FAST) and Global Deterioration Scale (GDS) [3.2a] [3.2b]

- Classify the severity of dementia resembling the reverse of child development.
- Both were developed by Reisberg in the 80's when Alzheimer's Disease was at the centre stage in the field of dementia research. FAST follows the same staging system as in GDS with addition of sub-staging in stage 6 and 7.
- The staging system is useful in 2 aspects:
  - It describes longitudinally the progressive functional deterioration in Alzheimer's disease from onset to end stage. "what will happen to me/the patient?" is a common question from the caregivers or the patients themselves. FAST can provide information to answer this question. The information will assist in advance directives and other social and financial planning.
  - It helps to improve diagnostic accuracy. If the history of illness shows prominent deviation from the progression as described in the GDS/FAST, we should review our diagnosis. For example, early manifestation of motor/incontinence symptoms will make the diagnosis of AD unlikely.

3.2.2 Clinical Dementia Rating (CDR) [3.2c]

- 5-point scale to categorize Alzheimer's disease:
  - 0: Normal
  - 0.5: Very Mild Dementia
  - 1: Mild Dementia
  - 2: Moderate Dementia
  - 3: Severe Dementia
- Assesses memory, orientation, judgment and problem solving, community affairs, hobbies and personal care.
- Each domain classifies into questionable (score 0), mild, moderate and severe (score 3).
- Is often used in drug trials for staging of dementia and requires input from both the patient and the caregiver.

- As it may take up to 45 minutes to administer, it is not practical in most clinic situation. However, the structure and items in the CDR serves as a very good backbone for history taking in dementia, especially for trainees and colleagues new to the field.
- Free training for the CDR is available on the web at. [3.2d]

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3.3 Scales for Functional Assessment

In usual clinic settings a scale for evaluation of ADLs or IADLs is not an absolute necessity. There is a tendency to focus on cognitive status for treatment/disease monitoring in dementia. However, functional limitations should never be left out, because they are often more related to caregiver burden. The indication of most if not all current dementia drugs are to delay cognitive decline and maintain ADL independence. Knowing which ADL items to observe and how to monitor changes in these ADLs is important for treatment monitoring and communicating with the caregiver.

3.3.1 The Chinese Version of the Disability Assessment for Dementia (CDAD) [3.3a]

- Takes ~15 minutes to administer.
- Assesses functions on both ADLs and iADLs, e.g. personal hygiene, dressing, toileting, eating, meal preparation, using telephone, going out, financing, medication management, housework and entertainment. Whereas both the BI and the Katz were designed to measure basic ADLs only, and are not specific for dementia. The BI measures independency in 10 basic ADLs, and the Katz measures independency in 6 basic ADLs. The BI has a score ranging from 0-100, hence is more sensitive to changes and is used more often in rehabilitation settings. The Katz ranges only from 0-6, is less sensitive to changes, but is very simple to use, and therefore more often used to assess stable nursing home residents.
- Scores are given to what the individual is actually doing instead of what s/he can do, e.g. score will be given if the individual is taking a pill correctly without any reminder (no score if the individual takes the pill on prompting).
- Being specific to dementia patient, it addresses problems commonly encountered in dementia:
  - Initiation: It asks whether the patient decides to take a bath on his/her own. For example, the DAD asks whether the patient decides to take a bath or wash his/her hair on his/her own, while the BI and Katz only ask whether he/she can bath his/herself with or without assistance. The lack of initiation is a hallmark of dementia. In someone with dementia, being able to decide to take a bath without being reminded to is very different from doing so only with prompting or coercing.

- Judgement: It asks whether the patient can choose appropriate clothing for the occasion or weather, in addition to being able to dress properly. The BI and Katz only assess whether the patient can dress him/herself or not.
- Memory: It asks whether the patient can take down or convey a telephone message. Memory is not assessed by the BI/Katz. In fact, none of the basic ADLs assessed by the BI/Katz requires much memory.

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3.4 Scales for Neuropsychiatric Symptomatology and Caregiver Burden in Dementia

3.4.1 Neuropsychiatric Inventory (NPI) [3.4a]

- It is one of the most frequently used tools in assessing BPSD.
- It assesses 12 psychiatric symptoms namely delusion, hallucination, agitation/aggression, mood (anxiety, depression, euphoria/apathy), disinhibition, irritability, aberrant motor behavior, sleep and eating problem.
- It takes 30-45 minutes to administer and is often used in drug studies.
- The higher the score means the more severe BPSD.
- The list of BPSDs in the NPI are very useful reminders for clinicians during history taking in dementia care.
- As BPSDs are often highly related to caregiver stress, noting the type, severity and frequency of BPSDs, and the follow-up of their progress after treatment is important in relieving caregiver burden, allowing the patient to be cared at home longer, or causing less conflicts in institutions.
- Low overall NPI score does not mean low caregiver burden, e.g. patient with a high score on any one of the symptoms but low scores in the other symptoms could still be very challenging to the caregiver.

3.4.2 Zarit Burden Index [3.4b] [3.4c]

- It is a popular caregiver self-report measure for use in clinical or community settings.
- It has been specially designed to reflect the stresses experienced by the caregiver of patients with dementia.
- It originated as a 29-item questionnaire but the revised 22-item version is more commonly used.
- It covers areas of concern mostly mentioned by caregiver, including caregiver's health, psychological well-being, social life, finance, and the relationship between the caregiver and patient. Each item is a question which the caregiver is asked to endorse using a 5-point scale. Response options range from 0 (never) to 4 (nearly always). It is scored by adding the numbered response of the individual items. The total score ranges from 0-88. The higher score means the higher level of caregiver burden.

- It is suggested that a score below 21 indicates little or no burden, 21-40 for mild to moderate burden, 41-60 for moderate to severe burden, and 61-88 for severe burden.
- The Chinese version of ZBI was validated in Hong Kong in 2005. [3.4d]

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3.5 Screening Tool for Depression in Dementia

3.5.1 Cornell Scale for Depression in Dementia (CSDD) [3.5a]

- Takes ~20 minutes to administer.
- It is specifically designed to detect the signs and symptoms of depression in patient with dementia by using both patient-provided and caregiver-provided information are used. It has the advantage of not relying solely on the recall or opinion from dementia patients.
- The CSDD is a semi-structured interview and not a questionnaire. Therefore, it also relies on observation of the patient in the clinic (e.g. fidgeting or looking sad) rather than just the yes/no answer given.
- In contrast to the Geriatric Depression Scale (GDS) which is a screening test, the CSDD score does indicate different levels of severity. Full score is 38. A score >10 indicates probable major depressive episode, >18 indicates definite major depressive episode.
- In contrast to the GDS, the CSDD also addresses biological symptoms (e.g. appetite, sleep and diurnal mood variation) and behavioral symptoms (e.g. agitation, motor retardation and multiple somatic complaints) that could be observed by the caregivers. The GDS addresses subjective feelings which might not be presented accurately by dementia patients.
- It uses simple language such as “are you feeling sad” or “no good”, rather than exploratory questions such as “do you feel there is no hope in your life”. The latter may be too abstract for dementia patients.

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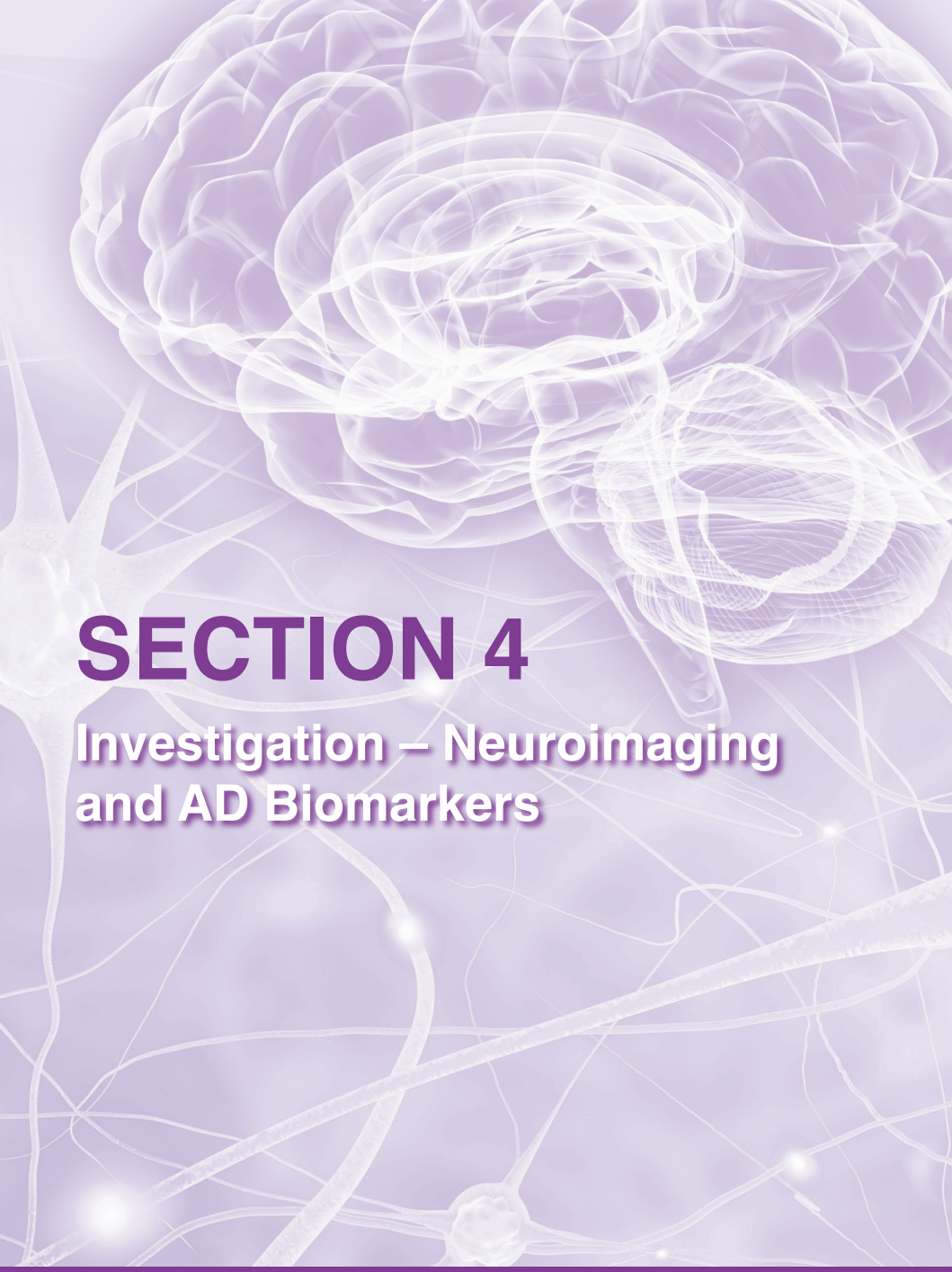


SECTION 4

Investigation – Neuroimaging and AD Biomarkers

4.1 Neuroimaging [4.1a] [4.1b]

4.1.1 Indications for Neuroimaging in Dementia

- When clinical diagnosis is in doubt, e.g. Alzheimer's Disease vs. dementia with Lewy bodies, depression vs. pseudo-dementia
- When organic disease is suspected, e.g. recent onset of signs and symptoms, history of head injury, acute delirium
- When result of neuroimaging affects clinical management

4.1.2 Imaging Modalities

Neuroimaging in dementia consists of structural imaging by high-spatial-resolution MRI and implementation of pathophysiology-specific radiotracers molecular imaging in nuclear medicine. The radiologic and nuclear medicine modalities are complementary. By using an integrated approach with the clinical presentation, early diagnosis can be achieved, giving patients and families an opportunity to confront the disease and start earlier management.

Structural Imaging

- CT brain (non-contrast) is the baseline imaging to exclude most of the organic causes, e.g. small vessel disease, hydrocephalus, infarctions and hemorrhage, subdural collection and space-occupying lesions.
- MRI brain (non-contrast) is better than CT brain in terms of lesion characterization. It allows more in-depth assessment for region- or lobar-specific patterns of brain volume loss (including specific structures such as hippocampus, entorhinal cortex and precuneus) by multi-planar assessment. These patterns are critical in differentiating the neurodegenerative diseases.
- Serial comparison is essential to find out the dominant lobar atrophy in various dementias or minimal progression in age-related cerebral atrophy.

Molecular Imaging

Fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)

- The most common contrast agent used in modern PET.
- It allows visualization of the functioning cerebral cortex, and show the distribution of metabolic derangements which allows differentiation of disease processes in the same manner as that of structural MRI. FDG PET may potentially identify early abnormalities that have not yet manifested in structural change.

Amyloid-β PET

- This group of contrast agents allows visualization of abnormal amyloid aggregation. At β-amyloid imaging, normal white matter takes up these agents. Areas of increased cortical uptake are considered abnormal and correspond to cortical deposition of β-amyloid plaques.
- Only able to confirm or exclude AD, sometimes DLB, but not others.

^{123}I-Ioflupane SPECT

- Commercially referred to as DaT scan (GE Healthcare)
- Parkinsonian-type diseases shares a similar pathophysiology with loss of dopaminergic neurons which predominantly clustered in substantia nigra and corpus striatum. This imaging allows the visualization of decreased or absent radiotracer accumulation in corpus striatum.
- Normal distribution of radiotracer has a comma appearance with curved uptake in caudate heads and putamina. Patients with parkinsonian disease begin with loss of putamina, resulting in a “period” OR “full stop” appearance, which can progress to almost complete loss of uptake.
- Decreased uptake in Parkinsonian-type diseases and DLB.
- Not helpful in differentiating between Parkinson’s disease and atypical parkinsonism
- Useful in differentiating AD (normal) from DLB (decrease uptake) when clinically difficult

4.1.3 Specific Dementia Syndromes/Neurodegenerative Diseases

Alzheimer's Disease

- MRI and FDG PET: atrophic change and hypometabolisim in the parietotemporal distribution with predilection for the posterior cingulate gyrus, mesial temporal lobe and precuneus, with sparing of the sensorimotor strip and occipital region
- Amyloid PET: abnormal amyloid tracer uptake symmetric and diffusely within the cortex (loss of grey-white differentiation)
- ^{123}I-Ioflupane SPECT: normal uptake

Frontotemporal Lobar Degeneration (FTLD)

- Based on clinical presentation, FTLD can be divided to behavioral variant and primary progressive aphasia (PPA), the dominant patterns of regional atrophy and hypometabolism are different for various subtypes.

Subtype	MRI and FDG PET
Behavioral variant FTD	Bilateral frontal lobes
PPA	
Semantic variant PPA	Left temporal lobe
Non-fluent variant PPA	Left insula and frontal opercula
Logopenic variant PPA	Left temporo-parietal junction

- Relative sparing of parietal lobes
- Hippocampal atrophy is not dominant in early to moderate FTD when compared with dominant temporal lobe atrophy, but eventually will become significant in moderate to severe stage of FTD
- Usually asymmetrical atrophy, that can be used to differentiate FTD from AD
- Amyloid PET: no abnormal uptake. It can be used to differentiate between FTD and AD.

Vascular Dementia

- MRI and FDG PET: evidence of vascular insults, including encephalomalacia from multiple vascular territory infarcts, small vessel disease with diffuse confluent periventricular hypodensities on CT or hyperintensities on T2W MRI, lacunar infarcts.
- May associate with global cerebral atrophy
- Ventriculomegaly proportional to cerebral atrophy
- ^{123}I-Ioflupane SPECT and amyloid PET: no abnormal uptake

Dementia with Lewy Bodies

- MRI and FDG PET: cortical loss and hypometabolism classically beginning in the occipital lobes, asymmetric hypometabolism in the frontotemporal lobes similar to that depicted in AD. There is sparing of the posterior cingulate gyrus (also known as "cingulate island sign") which is invariably involved in AD.
- MRI: absent swallow tail sign (absence of normal high signal intensity) on susceptibility weighted images at nigrosome 1 in substantia nigra is reported to have high diagnostic utility in parkinsonian neurodegenerative diseases and can supportive of a DLB diagnosis.
- ^{123}I-Ioflupane SPECT: decrease/loss of striatal uptake in DLB, but not in AD.

Other Parkinson Plus Syndromes

Progressive supranuclear palsy

- MRI: pronounced atrophy of midbrain (hummingbird sign in MRI) which accounts for the typical vertical/downward gaze paralysis
- FDG PET: decreased uptake in the posterior frontal lobes, mid-brain and basal ganglia
- ^{123}I-Ioflupane SPECT: symmetric or asymmetric decreased striatal activity

Multiple system atrophy

- ^{123}I-Ioflupane SPECT: symmetric or asymmetric decreased striatal activity
- MSA-P: low T2W signal at dorsolateral putamen and slit-liked increased signal lateral to putamen on T2W (putaminal rim sign)
- MSA-C: disproportionate atrophy of cerebellum and brainstem (especially olivary nuclei and middle cerebellar peduncle), hot cross bun sign at pons

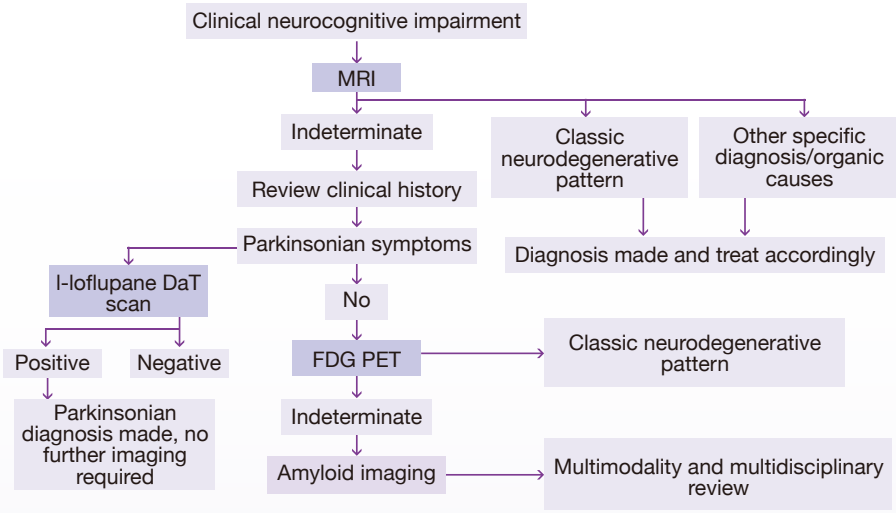
Corticobasal degeneration

- MRI and FDG PET: asymmetrical parietal and/or frontal cortical atrophy/hypometabolism, sometimes associated with hyperintensity of white matter on T2W images
- ^{123}I-Ioflupane SPECT: decreased striatal activity (usually asymmetrical)

Normal pressure hydrocephalus

- Ventriculomegaly disproportional to cerebral atrophy
- Presence of prominent CSF flow void at the level of third ventricle, cerebral aqueduct and fourth ventricle, suggestive of increased velocities and excluding obstruction. CSF flow study may also be used to support the diagnosis.

4.1.4 Patient Workup and Algorithm



4.1.5 Brain Region Atrophy and Differential Diagnoses

Brain Region	Differential Diagnoses
Frontal lobes atrophy	FTLD, FTD, non-specific atrophy
Temporal lobes atrophy	AD (symmetrical), FTD, PPA, CBD (asymmetrical)
Hippocampal atrophy	AD (symmetrical) usually not significant in early FTD
Parietal lobes atrophy	AD and non-specific age related atrophy less prominent in FTD
Occipital lobes atrophy	Usually not prominent unless in moderate or severe stage of dementia, if occurs in early stage, DLB is suspected
Brainstem atrophy	PSP, MSA
Cerebellum	Alcoholism, MSA-C
Periventricular regions	Small vessel disease (SVD) vs. NPH
Basal ganglia	More than 5 infarcts in SVD

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4.2 AD Biomarkers

- Biomarkers are parameters that can be measured in vivo to reflect specific pathophysiological processes. Neuroimaging, cerebrospinal fluid (CSF) assays, and other biomarkers now can detect evidence of the AD pathophysiological process in vivo without autopsy.
- Pathophysiological process of AD, measurable by biomarkers, begins years before the diagnosis of clinical dementia, which extends the spectrum of AD to a preclinical phase.
- It is hypothesized that biomarkers of AD neuropathology become abnormal in an ordered pattern:
  1. Aβ accumulation (PET, CSF)
  2. followed by synaptic dysfunction (functional MRI, FDG PET)
  3. tau-mediated neuronal injury (PET, CSF)
  4. brain structure alteration (volumetric MRI)
  5. cognitive impairment
  6. clinical (daily activities) manifestation

4.2.1 Biomarkers and Diagnostic Criteria of AD

In 2011, NIA-AA formally incorporated five most widely studied biomarkers of AD into the diagnostic criteria:

1. The biomarkers of Aβ accumulation:
   abnormal tracer retention on amyloid PET imaging and low CSF $A\beta_{42}$.
2. The biomarkers of neuronal degeneration or injury:
   - elevated CSF tau (both total tau (T-tau) and phosphorylated tau (P-tau));
   - decreased FDG uptake on PET in a specific topographic pattern involving temporo-parietal cortex; and
   - atrophy on structural MR again in a specific topographic pattern involving medial, basal and lateral temporal lobe, and medial and lateral parietal cortices.

- In the preclinical phase biomarkers are used to establish the presence of AD neuropathology, intending purely for research purposes.
- In clinical phase, both the MCI and AD dementia, clinical diagnoses are paramount and biomarkers are complimentary.
- In MCI phase, biomarkers are used to establish the underlying etiology.
- In the dementia phase, biomarkers are used to increase or decrease the level of certainty that AD neuropathology underlies the dementia.
- Biomarker severity, particularly neuronal injury biomarkers, also indicates the likelihood of imminent progression to AD dementia.

In 2018, NIA-AA established a research framework grounded entirely on a biomarker-based biological definition of AD in living people. It is not a diagnostic criteria or clinical guidelines and is intended for research purpose purely.

- Neurodegeneration is not specific for AD and therefore biomarkers of neuronal injury are not placed on equal footing with biomarkers reflecting amyloid and pathologic tau accumulation as they were in the 2011 guidelines.

- Biological definition of AD
  The fact that an amnestic multi-domain dementia is neither sensitive nor specific for AD neuropathologic change suggests that cognitive symptoms are not an ideal way to define AD.

- NIA-AA therefore recommends employing biomarkers to define the disease entirely without clinical phenotype, which shifts the definition of AD in living people from a syndromal to a biological construct.

- Biomarkers that are specific for the hallmark of AD proteinopathies (i.e. Aβ and pathologic tau) are considered as the biomarker definitions of the disease.

- AT(N) Classification
  In the NIA-AA research framework, the AT(N) Classification System was adopted to group different biomarkers (imaging and bio-fluids) by the pathologic process each measures

AT(N) biomarker grouping	
A:	Aggregated Aβ or associated pathologic state CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio Amyloid PET
T:	Aggregated tau (neurofibrillary tangles) or associated pathologic state CSF P-tau Tau PET
(N):	Neurodegeneration or neuronal injury Anatomic MRI FDG PET CSF T-tau

Regarding tau, it separates biomarkers that are specific for pathologic tau (CSF P-tau and Tau PET) from those that are non-specific measures of neurodegeneration/neuronal injury (CSF T-tau). This represents a major change from the biomarker grouping in 2011.

Indicators of neurodegeneration or neuronal injury are not specific for neurodegeneration due to AD. Therefore (N) is placed in parenthesis, indicating the fundamental differences between (N) and AT. The (N) biomarker group provides important pathologic staging information.

Note that either using CSF or imaging biomarker alone can complete the biomarker characterization.

4.2.2 Clinical Interpretation and Application

- Much tighter correlation between neurofibrillary pathology and cognitive impairment than between amyloid pathology and cognitive impairment.
- Neurodegeneration, however, is most closely coupled with cognitive impairment.
- Biomarkers can help detection of the pre-clinical phase of the disease, staging the disease severity and progression and certainty of diagnosis.

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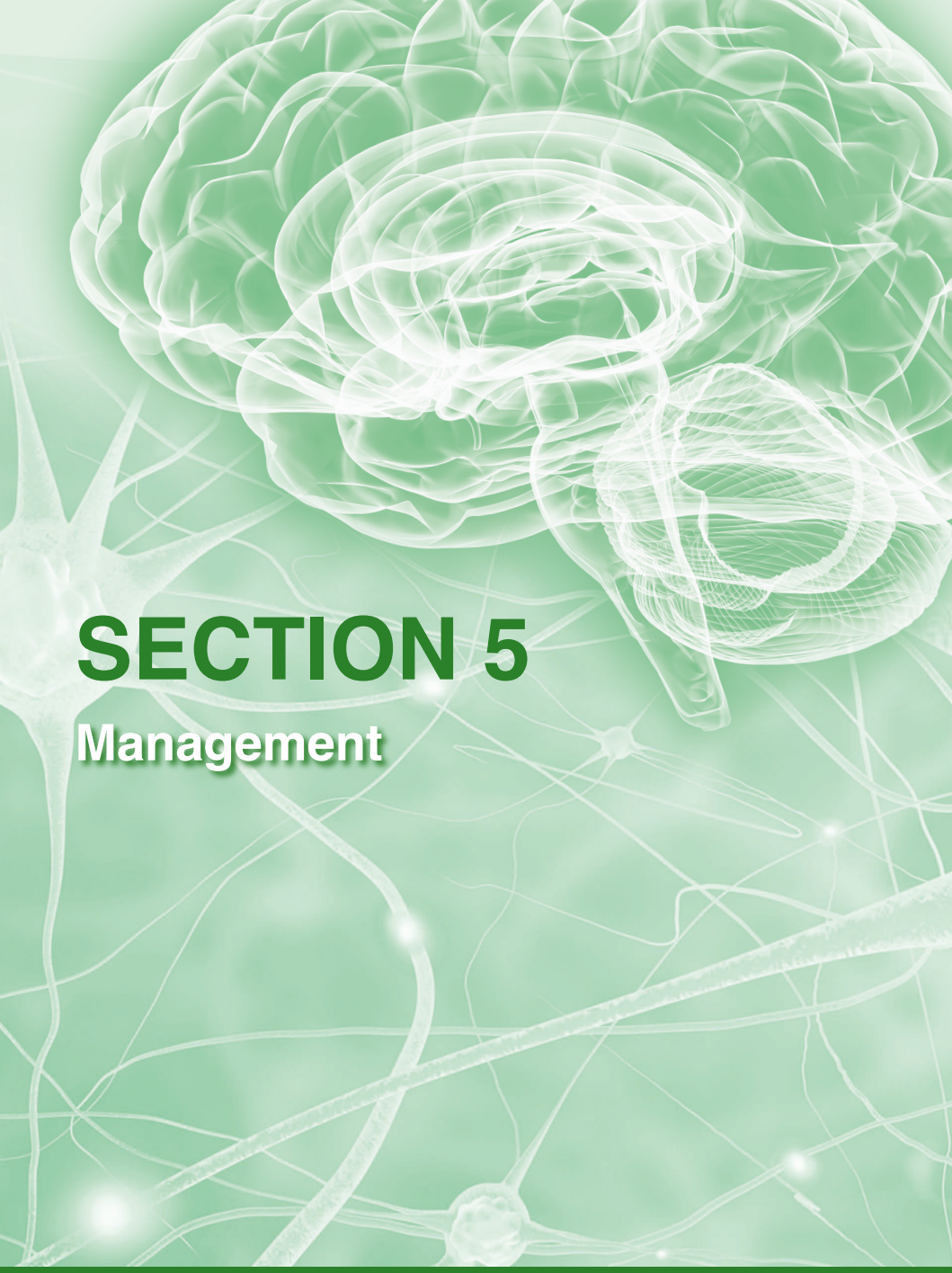

SECTION 5

Management

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Management

5.1 Non-Pharmacological Management of Behavioral and Psychological Symptoms of Dementia (BPSD)

The International Psychogeriatric Association (IPA) Consensus Conference in 1999 produced a statement on the definition of BPSD which refers to the non-cognitive symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia.[5.1a] Those symptoms are called neuropsychiatric symptoms which include behavioral and psychological aspects:

1. Specific behavioral symptoms: usually identified on the basis of observation of the person with dementia, e.g. wandering, agitation, disinhibition, catastrophic reactions, complaining and negativism.
2. Specific psychological symptoms: usually and mainly assessed through interviews with persons with dementia and their relatives, e.g. delusion, hallucination, misidentification, depression, apathy and anxiety.

5.1.1 Assessment

Please refer to Section 3: Assessment Scales in Neurocognitive Disorders for BPSD assessment tools: [5.1b]

1. Chinese version of the Cohen-Mansfield Agitation Inventory (CMAI) [5.1c]
2. Chinese version of the Neuropsychiatric Inventory (CNPI) [5.1d]
3. Clifton Assessment Procedures of the Elderly (CAPE) [5.1e]

5.1.2 Approach of Identifying Underlying or Modifiable Cause of BPSD

1. "ABC" Approach: developed to identify the underlying or precipitating cause, characterize the behavior and its consequence.
   - **A**ntecedent: preceding events; who, how, what, where, when, why the BPSD occurs
   - **B**ehavior: problem behavior; the type or characteristics of BPSD
   - **C**onsequence: consequent events; the outcome and effect of BPSD on patient, caregiver and the environment

ABC are analyzed and hypothesis-driven interventions are derived. Family and staff caregivers are trained and supported to apply these individually tailored hypothesis-driven interventions. The intervention is monitored and provide information to the therapist to evaluate the progress.

2. "TECH" Approach: developed by Sharon Kratiuk-wall (1996) is also recommended.[5.1f] It provides a systematic and structured way to determine the triggering factors of BPSD by asking 4 key questions. Those questions are broken down into four headings: **T**ask, **E**nvironment, **C**ommunication and **H**ealth status, as follows:

Task	Environment	Communication	Health Status
• Too many choices? (limit ability to process information) • Task too complex? • Too many steps? • Difficulty in recognition or familiarity? (e.g. object) • Is the task reminiscent of past pleasant / unpleasant experiences?	• Provide safety and security? (Physical and emotional) • Too much / too little stimulation? • Too much / too little space? • Appear unfamiliar? • Appear reminiscent of past unpleasant experience? • Optimum for function? e.g. temperature, lighting, seating, etc. • Structure to allow participation? • Provide cues for activity?	Is there a need to: • Focus on the feelings underlying a person's words? • Reduce complexity of the communication? • Place emphasis on non-verbal communication? • Be calmer, quieter, less demanding • Minimize distraction?	Is the behavior related to: • Cognitive deficit? • Aging e.g. hearing, sight, change of sleeping pattern? • Medication? • Fatigue? • Hunger or thirst? • Constipation? • Pain or discomfort?

Under each key question, not only the possible causes considered to be triggers to the person's behavior are analyzed, but a framework to tackle the BPSD is also provided.

5.1.3 Categories for Non-Pharmacological Interventions for BPSD

For both professional group therapy and individual therapy, it is generally agreed that non-pharmacological interventions should be considered as the first-line management of most BPSD.[5.1g] [5.1h] Although a number of non-pharmacological interventions (see table) are now available for persons with dementia, it should be noted that there are several areas of overlap between these therapies and, in fact, each approach is rarely used in isolation. Client-centered and tailored therapy guided by the patient's background, interests, cultural, religious and life factors to the person with dementia are the most important concept in treating one's BPSDs.

Category	Intervention
Sensory-oriented	Multi-sensory stimulation
	Music activities/therapy
	Touch/massage
	Aroma therapy
Activity-oriented	Cognitive Stimulation Therapy (CST)
	Montessori Methods for Dementia (MMD)
	Reality orientation
	Reminiscence activities/therapy
	Art therapy
	Doll-therapy
	Recreational activities
	Outdoor walks
	Physical activities
	Simulated interactions/family videos
	Pet therapy/animal-assisted therapy
	Pet robot intervention
Communication-oriented	Validation therapy
	Communication and management techniques
Environment-oriented	Environmental modification
	Controlled stimulation
	Activity scheduling
	Wandering areas
	Light therapy

Montessori materials consist of “learning games” suited to a patient’s abilities and interests, examples are memory games, household utensils, books and so on.[5.1i] The aim of the Montessori Method for dementia is to provide opportunities for the patient to enjoy life by engaging in daily roles, routines and activities of daily living that are created and presented based on his/her needs, strengths, skills, abilities and interests, and delivered in a supportive environment purposefully and meaningfully. The rationale is that undesirable behavior would be significantly decreased when the patient’s unmet needs are met. [5.1j]

National and international guidelines often recommend non-pharmacological interventions as the first line of treatment for BPSD. However, there is evidence that anti-psychotic medications can also be used effectively when the BPSD poses significant risks of harm to the patient or others, or when the aggressive symptoms are persistent, recurrent or severe enough to cause significant suffering and distress.

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5.2 Non-Pharmacological Cognitive Intervention

Though research finding is yet to be conclusive, the concepts of neuroplasticity and cognitive reserve have gained increasing attention as potential factors for delaying cognitive decline associated with aging or injuries.

There are 2 types of intervention: direct cognitive intervention and cognitive intervention via physical training.

5.2.1 Direct Cognitive Intervention

1. Types of non-pharmacological cognitive interventions [5.2a]
   i. Cognitive stimulation: non-specific exercises focusing on cognitive and social functioning reinforcement. Some examples include discussions, reminiscence therapy, reality orientation. Positive effect on cognition of people with mild to moderate dementia was demonstrated under this intervention. [5.2b]
   ii. Cognitive training: through structured and guided practice aiming to maintain or improve a particular aspect of cognitive functioning such as memory or attention. Difficulty levels are constantly adapted in response to the person's performance and progress. This intervention was found to improve the general cognitive functioning of people with mild dementia. [5.2c]
   iii. Cognitive rehabilitation: this person-centered intervention focuses on improving or maintaining cognitive abilities related to a person's everyday needs so to facilitate independent living. It was shown to be able to slow down the progression of cognitive decline in people with dementia and was considered as one of the most effective cognitive interventions. [5.2d] This intervention might include the use of:
      a. Environmental support: environmental modification
      b. Use of external devices: to help increase independence, e.g. efficient bathing or other self-care, to provide reminders, to facilitate communication
      c. Self-management strategies: orientation procedures, awareness enhancement, procedural training, pacing, key ideas log, etc.

2. Other therapy components which might affect the progress of the cognitive interventions and therefore should also be considered.
   i. Motivational and affective issues: emotion regulation strategies and behavioral activation strategies might be used to enhance motivation and regulate emotion. Counseling or psychotherapy might also be considered when needed.
   ii. Caregiver support: support could be offered to enhance caregiver's understanding of the sources of stress, and to identify strategies for more effective stress management. If the caregiver is ready and willing, with enough caregiver training, education and support, caregiver could also participate and offer support in the cognitive interventions.
   iii. Learning and information retention ability: reference could be made to the neuropsychological assessment results on the person's cognitive profile in learning. Goals of the cognitive intervention could be adjusted accordingly.
   iv. Ability to generalize: the person's ability to generalize the trained skills or apply the skills into the person's daily living should be monitored. The goals of the cognitive interventions could then be adjusted accordingly. For example, whether there is spontaneous use of learnt skills or compensation strategies, ability to use the skills or strategies with reminder or active facilitation, inability to use them albeit active facilitation.
   v. Signposting to other sources of support: this might include community support to ease caregiver's stress, provide social environment, aids/device loaning, financial support.

5.2.2 Cognitive Intervention Via Physical Training

Various exercise approaches can augment the cognitive function of patients with mild cognitive impairment.

Aerobic exercise training is well known for its effects on improving cognitive function by enhancing cerebral blood flow, oxygen extraction, glucose utilization and activation of growth factors for capillary vascularization. Moderate intensity aerobic exercise may increase the hippocampal and cortical volume. It also promotes positive neuroplasticity by facilitation of new and stronger neural connection.

The ability of multi-tasking is essential for carrying out activities of daily living. Simultaneous execution of motor and cognitive tasks, such as doing calculation or naming during walking, is the strategy employed in dual-task training.

Multiple sensorimotor components to address balance, posture and coordinate skills associated with daily activities focus on working between the 3 planes in relation to the body's vertical axis. It provides spatial orientation training that allows gaining attention and motor memorization. Those cross-midline exercises enhance communication between left and right cerebrum.

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5.3 Pharmacological Management

5.3.1 Treatment Guideline and Practical Tips in Using Cognitive Enhancers - Cholinesterase Inhibitors, NMDA Receptor Antagonists and Anti-Amyloid Target Therapy

Alzheimer's disease is complex, multifactorial and progressive in nature. Non-pharmacological means to enhance the coping skills for the patients and caregivers should be optimized at all times and all stages of the disease. Three broad categories of treatments consist of (A) symptomatic cognitive enhancers to slow progression of AD, namely cholinesterase inhibitors (ChEIs), N-methyl-D-aspartate (NMDA) antagonists and their combination; (B) therapies targeting amyloids, such as adacanumab; (C) pharmacological therapies for behavioral and psychological symptoms of dementia (BPSD) are covered in Section 5.3.2: Pharmacological Management of BPSD. Please refer to Section 5.3.2 for details.

Other emerging therapies such as anti-oxidants, target therapy against tau protein, anti-neuro-inflammation, etc. are being trialed in ongoing studies.

Symptomatic Therapies for AD - Cognitive Enhancers

For MCI, a systemic review for the efficacy and safety of ChEIs or memantine found no significant effects on cognition or function. However, higher rates of nausea, diarrhea, vomiting, and headache in treatment group compared to the placebo group were observed. [5.3a]

For AD, ChEIs (donepezil, rivastigmine, galantamine) provide modest symptomatic benefit in a proportion of AD patients. All 3 drugs are approved for mild-moderate AD, only donepezil is approved for severe AD. The three ChEIs inhibit acetylcholinesterase (AChE) at the synapse (specific cholinesterase), thus improving cholinergic transmission, with similar efficacy.

The degree of benefit is summarized by a meta-analysis of 13 randomized trials of ChEIs vs. placebo in patients with mild to moderate AD. When assessed at 6 to 12 months, cholinesterase inhibitors led to modest cognitive improvements on the ADAS-Cog (mean difference 2.7 points) and MMSE (mean difference 1.37 points) as well as global impression by caregivers and ADLs. [5.3b]

This is equivalent to preventing a two-months-per-year decline in a typical patient with AD [5.3c] with modest beneficial impact on neuropsychiatric and functional outcomes for patients with AD. The numbers needed to treat (NNT) are 12 for one additional patient for minimal improvement or better and one would develop a treatment-related adverse effect. NNT for stabilization or better is 7 and NNT for marked improvement is 42. [5.3d] The evidence for long term outcomes such as nursing home placement or disability progression is inconclusive.

These findings remind us to individualize decisions for each patient based on clinical response and side effects.

Donepezil (Aricept)

Donepezil has shown efficacy in patients with mild, moderate and severe AD. Donepezil's long half-life provides a long duration of drug availability for binding at the receptor sites. Dosing recommendations for mild to moderate AD are 5-10 mg given once daily.

High dose donepezil 23 mg once daily in a study involving 1467 randomized patients with moderate to severe Alzheimer's disease found a significantly greater cognitive benefit on the Severe Impairment Battery (SIB) after 6 months of treatment as compared with patients who continued taking donepezil 10 mg/day. Improved cognition and global functioning at week 24, were assessed using least squares mean changes from baseline on the Severe Impairment Battery (SIB; cognition) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input scale (CIBIC+; global function rating). [5.3e]

However, be cautious of side effects in using high dose ChEI, in particular for low BMI patients who are commonly intolerant. Slow and cautious upward titration to the maximum dose is recommended.

Rivastigmine (Exelon, Exelon Patch)

Rivastigmine is a potent, selective inhibitor of brain AChE and BChE. Rivastigmine is considered a pseudo-irreversible inhibitor of AChE. Oral rivastigmine is indicated for the treatment of mild to moderate dementia of the Alzheimer type. Initial dosing recommendations are 1.5 mg PO BID, with a maximum dose of 12 mg/day PO. Rivastigmine has added indication for treating

mild to moderate dementia associated with Parkinson's disease. Rivastigmine is contraindicated for patients with severe hepatic impairment.

The transdermal patches 4.6 mg/24h and 9.5 mg/24h are approved for mild to moderate AD patients. It has the advantage of less gastrointestinal side effect, better 24 hours drug profile and easier to administer to patients. Yet, mild dermatitis is not uncommon at the applied sites of patches. A reliable caregiver has to be committed to removing the old patch before a new patch is applied daily.

A high dose 13.3 mg/24h rivastigmine transdermal patch for patients with mild, moderate and severe Alzheimer's disease is available for those with a decline in overall function and cognition. Based on the 48-week double-blind OPTIMA study, mild to moderate AD patients on the 13.3 mg/24h dose experienced significantly improved overall function compared with those on the 9.5 mg/24h patch ($P<0.05$), as measured by the Alzheimer's Disease Cooperative Study Instrumental Activities of Daily Living (ADCS-IADL) scale at week 48. There was significant improvement in cognition as measured by the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) at 24 weeks but not at 48 weeks. In patients with severe disease, the ACTION (ACTivities of Daily Living and CognitION in Patients with Severe Dementia of the Alzheimer's Type) study, a randomized, double-blind trial found the 13.3 mg/24h dose patch when compared with the lower 4.6 mg/24h dose demonstrated statistically significant improvement in overall cognition and function in severe AD patients at week 24, as assessed by measures of cognition and daily function using the Severe Impairment Battery (SIB) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living–Severe Impairment Version (ADCS-ADL-SIV), respectively. [5.3f] [5.3g]

Galantamine (Reminyl PRC)

Galantamine is indicated for the treatment of mild to moderate dementia of the Alzheimer type. The dosing recommendation for the immediate-release formulation is 4 mg twice daily. The extended-release formulation is given at a dose of 8 mg once daily. The maintenance dose after dose titration is 16-24 mg/day.

Memantine (Ebixa)

Memantine is a N-methyl-D-aspartate (NMDA) antagonist, which by reducing neuronal calcium ion influx and its associated excitotoxicity and cell death, has proposed neuroprotective action for moderate to severe Alzheimer's dementia. It is an option for patients with moderate Alzheimer's disease who are intolerant of or have a contraindication to ChEI. A systemic review concluded that memantine improves cognition and global assessment of dementia with small effects of unclear clinical significance; and improvement in quality of life and other domains are suggested.

Memantine is approved for the treatment of moderate to severe AD. The initial dose for the immediate-release formulation is 5 mg once daily, and it can be titrated by 5 mg weekly to a maximum dose of 20 mg/day, usually in two divided doses. A tapering schedule with a similar timeline should be followed if memantine is to be discontinued.

Memantine has less side effects than ChEI. However, dizziness, confusion and hallucinations have been reported and may increase agitation and delusional behaviors in some patients with AD, and dementia with Lewy bodies.

Combination of ChEI and Memantine

The combination of memantine and a cholinesterase inhibitor may be used in patients with advanced disease with some studies reporting modest improvements in cognition and global outcomes, but the data is not conclusive.

AD Therapies Targeting Amyloid

Aducanumab is a recombinant monoclonal antibody directed against amyloid beta, recently approved by the US Food and Drug Administration (FDA) for the treatment of mild AD.

The two phase III trials (EMERGE and ENGAGE) which were terminated after a planned futility analysis. After continuing to collect data, nonetheless, it was possible to demonstrate EMERGE met its primary outcome but ENGAGE did not.

The primary outcome - Clinical Dementia Rating Sum of Boxes (CDR-SB) is a composite measure with cognitive and functional components including home activities, problem solving, and community engagement. In EMERGE, aducanumab treatment resulted in a significant 22% slowing of decline on the CDR-SB, which is of doubtful clinical significance. [5.3h] The 22% relative reduction correspond to an absolute difference of 0.39 in the CDR-SB score, is less than the usual score of 1-2 as the minimum clinically important difference. [5.3i]

In EMERGE, all secondary measures including the Mini Mental State Examination, Alzheimer's Disease Assessment Scale-cognitive subscale, and the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS ADL) scale showed statistically significant drug-placebo differences. The ADCS-ADL scale showed a 40% slowing of functional decline in the treatment group compared to the placebo group. The Neuropsychiatric Inventory (NPI) showed an 87% reduction from baseline scores in the high dose group of EMERGE. There was a corresponding 84% reduction in caregiver distress.

Amyloid plaques measured by amyloid positron emission tomography (PET) were markedly decreased by aducanumab in both trials. [5.3h]

The controversies which surrounded FDA approval can be referenced in various publications. [5.3i] [5.3j]

Due to lack of clarity in the clinical trials, adverse effects, and monitoring requirements, it is not presently recommended as routine treatment. The proposed appropriate use criteria [5.3k] states that aducanumab should only be considered for selected patients with MCI due to AD or mild AD itself, with proven amyloid pathology (by amyloid PET scan or lumbar puncture). Clinicians should discuss checking APOE allele status with patients before to initiating treatment, due to their higher risk of side effects. Brain MRI is needed at baseline and regularly for monitoring.

It is administered by intravenous (IV) infusion every four weeks. Duration of treatment with aducanumab is unclear, potentially if amyloid PET scan is negative or the patient has progressed to moderate dementia.

Patients should not be offered aducanumab if they have a high risk of hemorrhagic side effects, such as brain MRI with hemorrhagic findings on brain MRI (e.g. >4 microhemorrhages) and underlying brain lesion or vascular malformation. Other contraindications are conditions predisposing to increased risk of central nervous system (CNS) hemorrhage, such as anti-coagulant or anti-platelet use (other than aspirin 80 mg daily) and bleeding disorders.

The main side effect is amyloid-related imaging abnormalities (ARIA) which occurred in 40% on highest dose of aducanumab and the risk of ARIA is greater in patients with an APOE ε4 allele. ARIA can take the form of edema (ARIA-E) and/or microhemorrhage (ARIA-H), mainly asymptomatic, but may present with fatigue, headache, confusion, dizziness, falls, vision change, or nausea. In most patients ARIA-E resolves over time without long-term side effects; however, some patients experience a recurrence.

Practical Tips

- Before starting ChEI drug therapy, it is advisable to manage patient/caregiver expectations that these are symptomatic treatments and may only retard the disease progression without recovery. Moreover, not all patients are responders and treatment may be stopped if benefits are outweighed by harmful side effects. If the desired effects on stabilizing cognitive or other goals, e.g. target behaviors discussed with family are not perceived within a reasonable time period of e.g. 3-6 months, medications can be stopped.
- Target outcomes and monitoring - when treatment is initiated, it is key for physicians to gather caregivers' views on the patient's condition at baseline. Treatment should be continued only when it is considered to have beneficial effects on cognitive, global, functional or behavioral symptoms. Patients who continue on treatment should be reviewed regularly using appropriate cognitive, global, functional, and behavioral assessment tools.

- Adverse effects of ChEIs - educating patients/caregivers about the adverse effects of ChEIs is essential. They are generally mild and subside in a few weeks. Gastrointestinal effects such as anorexia, nausea, diarrhea and vomiting can occur in 20% of patients. Other adverse effects include bradycardia, syncope, incontinence, fatigue and insomnia. Caution if patients are on other heart rate slowing medications, sick sinus syndrome, cardiac conduction defects, history of obstructive airway diseases, overactive bladder, gastroduodenal ulcer diseases and hepatic impairment. Occurrence of resting tremor mimicking Parkinson's disease has been reported after ChEI therapy.
- Adverse effects of memantine - undesirable effects are dizziness, headache, constipation, somnolence and hypertension. Special precaution should be noted when prescribing the drug to patients with severe renal failure and patients with epilepsy.
- Starting and titrating - We start at low dose and titrate upwards within the first 3 months to the optimal dose which is usually lower than the recommended dose in most of the trials in western population. If one drug is not effective, some clinicians will switch to another class or another drug of the same class. Patch formulary may worth trying if there are GI side effects or tablet compliance issues. Combination therapy (ChEI together with memantine) may be an option if AD progresses to moderate or severe stage. Body weight and heart rate should be monitored.
- Stopping therapy - Considerations for stopping therapy are when harms exceed benefits, or when goals of maintaining function is no longer valid in advanced end-stage AD. ChEI dose should be slowly tapered before stopping. For medications for BPSD, regular gradual dose reduction may be considered as dementia advances because challenging behaviors previously encountered may have abated.

5.3.2 Pharmacological Management of BPSD [5.3l] [5.3m]

Pharmacotherapy not only can relieve the BPSD of patients but also can alleviate caregivers' stress and therefore may avoid institutionalization. However, to date, the evidence base for pharmacological management is inadequate and their use in BPSD is off licence. Therefore it must be tried after non-pharmacological methods fail and the BPSD are severe. The spectrum of BPSD is wide but that pharmacotherapy can only target part of the spectrum: apathy, aggression, agitation, anxiety, depression, psychosis and sleep cycle disturbance. When it is decided to be initiated, remember the 3Ts:

- **T**arget symptoms requiring treatment
- **T**itrate from a low starting dose watching for emerging adverse events
- **T**ime-limit prescriptions to avoid continuing ineffective treatment

  4 weeks to assess response

  3 months trial or withdrawal

BPSD is believed to be caused by neurotransmitter disturbance in people with dementia as illustrated below:

Over-activity of dopamine (DA) – psychosis

Over-activity of non-adrenaline (NA) – aggression

Underactivity of acetylcholine (Ach) – apathy and psychosis

Underactivity of serotonin (SRT) – depression and aggression

Understanding the relationship of neurotransmitter disturbance and BPSD is a pre-requisite in targeting the specific symptoms in BPSD by pharmacotherapy. There are broadly five classes of medications used in BPSD. They are:

1. Neuroleptics/anti-psychotics
2. Anti-depressants
3. Cognition enhancers
4. Mood stabilizers/anti-convulsants
5. Benzodiazepines

Neuroleptics/Anti-Psychotics

Neuroleptics or anti-psychotics act by suppressing dopamine over-activity in psychosis of dementia. The classical example is haloperidol, which was licensed to be used in schizophrenia. However, if being used in BPSD, the dosage needed is much lower. The main adverse effects include extrapyramidal effects (EPS), autonomic disturbance and anti-cholinergic (anti-cognitive) effects. It is not intended for long term use. The newer generation atypical neuroleptics, like risperidone or quetiapine act differently. They are SRT antagonists. Physiologically SRT induces increase in DA in the limbic system (and therefore improves depression) but reduces DA in cortico-frontal and nigro-striatal system. Therefore atypical neuroleptic via SRT antagonism can suppress DA excess (or psychosis) and increase DA in cortico-frontal region (improves negative symptoms) with less EPS by maintaining DA level in the nigro-striatal system. However it is worth noting that atypical neuroleptics are associated with significant risks:

1. Excess cerebrovascular risk
2. Early death within 12 months; may be related to long QT syndrome
3. Irreversible EPS and excess mortality in dementia with Lewy bodies (DLB) (Use rivastigmine and other means and then atypical neuroleptics as the last resort if BPSD is severe)

Anti-Depressants or Serotonin Reuptake Inhibitor (SSRI)

SSRI can relieve agitation with concomitant depression or dysthymia. It can also help aggression, impulsiveness and anxiety. Aggression or agitation in treated depression of AD patients may reappear paradoxically. It is mandatory to monitor sodium level (hyponatremia). Watch out for over-sedation and edema (mirtazapine). Remember serotonin syndrome (sweaty, tremoring/twitching, hypertension, tachycardia, fever, agitation or hallucination) can occur.

Cognition Enhancers

Ach underactivity causes apathy and psychosis and therefore cholinesterase inhibitors (ChEI) can attenuate these symptoms. ChEI is recommended as the first choice in all AD associated BPSD in non-urgent situation. Rivastigmine can be considered specifically for LBD. Memantine is indicated to treat BPSD in moderate to severe AD.

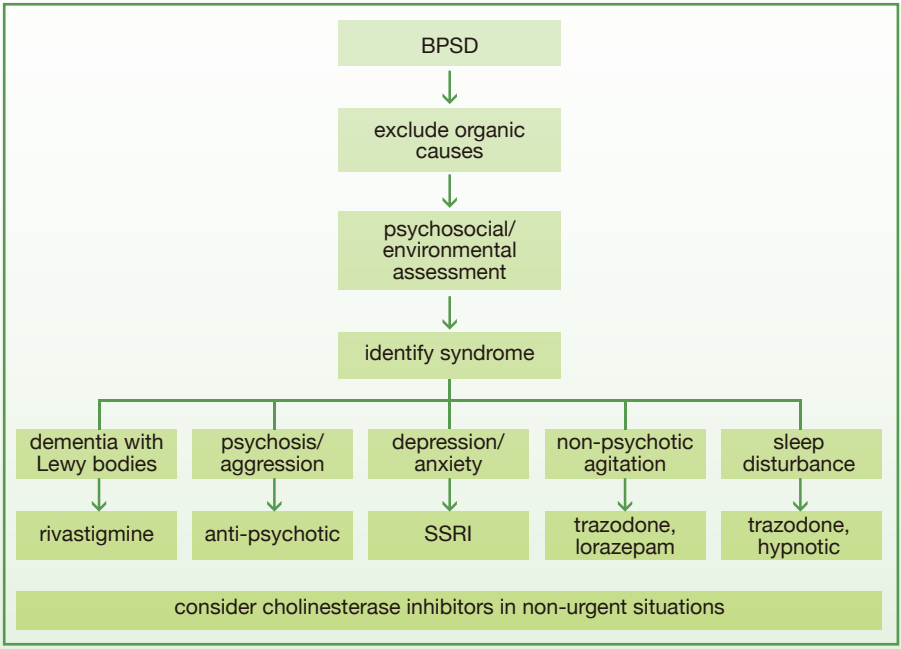
Benzodiazepines

They can alleviate anxiety, tension, irritability and insomnia. However, long term use is associated with cognitive and psychomotor detrimental side-effects. Beware of paradoxical disinhibition, which can be manifested as restlessness and agitation. Lorazepam or temazepam which have short half-life are preferred.

Anti-Convulsants and Mood Stabilizers

Carbamazepine, valproate, topiramate, lamotrigine, or gabapentin can target aggression associated with hyperactivity, pressured speech and expansive mood. Lithium is seldom used in older adults for neurotoxicity.

A pragmatic algorithm to manage BPSD is listed below for reference:



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SECTION 6

Late Stage Dementia

Section 6
Late Stage Dementia

6.1 End of Life Management in Late Stage Dementia

All dementia patients invariably will enter into the final stage. In this stage patients start to lose their mobility, speech, and finally, the praxis of basic activities such as walking, eating, and communication by facial expressions. Anti-dementia drugs become less useful in this stage, as there are no longer meaningful functions to be salvaged. The aim of management therefore will switch from cognition and function maintenance, to providing the patient with as much comfort as possible.

End of Life Care

Very few patients with early dementia would have considered how they would like to spend the last year of their lives. Often patients and families are engrossed in the loss of cognition and difficulties in daily activities in the earlier stages, without realizing that dementia and its complications lead to up to one-third of the deaths in developed countries. Being unaware and therefore unprepared, many patients with advanced dementia die with much suffering. In order to allow family caregivers, and certain early patients, to have an informed choice of end of life decisions, we must familiarize ourselves with some background knowledge.

When Does End of Life Begin?

Prognostication tools used for other diseases such as cancer or respiratory failure cannot be applied to patients with advanced dementia, because the disease trajectories are very different. The Gold Standards Framework (UK) [6.1a] used the following criteria for a life expectancy of approximately 12 months:

Triggers to consider that indicate that someone is entering a later stage are:

- Unable to walk without assistance and
- Urinary and fecal incontinence, and
- No consistently meaningful conversation and
- Unable to do ADL
- Barthel score <3/20

Plus any of the followings:

- Weight loss
- Urinary tract Infection
- Severe pressure ulcers – stage three or four
- Recurrent fever
- Reduced oral intake
- Aspiration pneumonia

In another cohort study, it was found that the clinical presentations of pneumonia, febrile illness other than pneumonia, or eating problems (including weight loss, swallowing or chewing problems, refusal to eat or drink, suspected dehydration, and persistently reduced oral intake) were the most common clinical events that signified the approach of the end of life phase in patients with advanced dementia. Having any of these events reduced the one-year survival by approximately half in these patients. The adjusted 6-month mortality rates after the occurrence of these events were 46.7%, 44.5%, and 38.6%, respectively. [6.1b]

These data should be able to provide a guide to prognostication in clinical practice.

End of Life Symptoms in Dementia

It is difficult to assess for end of life symptoms in dementia because most patients would have become non-communicable by then. Symptoms detection and relief therefore largely depends on the sensitivity of the caregiver and direct observation of behavioral changes in the patient. The most common symptoms listed in the literature include aspirations, pressure ulcers, dyspnea and pain. [6.1b] We must also remember that over-aggressive medical interventions such as invasive procedures and frequent blood-taking or instrumentation will also cause discomfort or even unnecessary risks. Restraints, often applied in relation to instrumentation such as tube feeding or intravenous fluid/medication administration, will always cause discomfort, immobility, and impair the quality of dying, in particular in the severely demented who cannot articulate their needs.

Detection of Pain in Advanced Dementia

Common tools for this purpose include:

- PAINAD (Pain Assessment in Advanced Dementia) [6.1c]
- NOPPAIN (Non-Communicative Patient's Pain Assessment Instrument) [6.1d]

These tools are based on observation of patient's body language, non-verbal vocalization and facial expressions, and can also be used for dementia patients other than those at the end of life.

Management of Pain or End of Life Symptoms

The management of these does not differ from those of cognitively normal patients. However, in face of increased irritability, one should not assume that it is delirium or BPSD. An active search for the cause of pain or discomfort should always be done as in good geriatrics practice: relief of bladder distension, constipation, itchiness or mal-placement of a limb can often improve the quality of dying for these non-communicable patients. A trial of analgesics or related medications can also be attempted if in doubt.

Feeding Problems in Advanced Dementia

Is tube feeding a good solution?

Feeding problems often herald the last stage of life in dementia. Common symptoms are slow eating, choking or coughing on or after eating, noisy breathing or wet voice, refusal to eat, or progressive weight loss. Eating problems are often due to dysphagia which is a part of the neurodegenerative process. Refusal to eat may be due to fear of choking with food, which the patient cannot communicate to caregivers, agnosia (when the patient cannot recognize food as food), or simply due to anxiety in unfamiliar surroundings or change of caregivers. Tube feeding is often used to manage feeding problems in advanced dementia. However, there is little evidence to support that tube feeding can improve survival, prevent aspiration pneumonia and prevent pressure ulcers. Yet there is ample evidence than tube feeding is associated with increased use of restraints and patient discomfort (including that due to force feeding such as abdominal bloating, and those due to the presence of the nasogastric tube, such as nasal/esophageal erosions, frequent tube replacement, reflux and associated pneumonitis/pneumonia). [6.1e]

Alternatives to Tube Feeding

Towards the end of life, the aim of feeding is no longer the maintenance of a balanced, healthy diet for healthy living. When both life expectancy and physical functioning becomes severely limited, the purpose of eating is to bring comfort and enjoyment. This view of feeding is also in line with the person-centered care approach in severe dementia.[6.1f] "Comfort feeding" is a term now adopted to describe careful hand feeding for end of life patients. Although it is difficult to assess patient satisfaction in advanced dementia, it is reasonable to believe that personal attention and tasty food provided by a kind face should be preferred over a tube and bottle hanging over the bed.

Problem	Possible Solutions
Choking, coughing	Upright positioning, chin-down head position, smaller spoon, thickened fluids, minced or puree texture
Wet voice	Prompt to swallow or cough, gentle throat stroking, change head position
Refuse eating	Modify environment, reduce disturbance in surrounding, improve food appearance or taste, favorite foods, favorite caregiver
Poor appetite/ early satiety	Rule out "pathology" from mouth to anus (oral ulcers, poor dental/oral hygiene, constipation), avoid over-sedation, reduce unnecessary medications ("pill burden")
Weight loss	Keep finger foods or favorite snacks at hand, frequent small high caloric-dense meals (forget about diet restrictions!)

Conclusion

End of life care and feeding problems in advanced dementia are quality of life (or death) issues. Medications are often not the mainstay of care, and as survival time is limited, invasive or over-zealous interventions should be avoided. Caregiver quality determines the quality of care. Therefore the task of the healthcare professional will have to change from "curative or preventive therapy" to caregiver education and support; and finally, symptoms relief for the patient in his or her last months or days.

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6.2 Advance Care Planning (ACP)

Comparing to the Advance Directive (AD) (please refer to Section 6.3: Enduring Power of Attorney, Guardianship Order and Advance Directive for details), an ACP is a much wider yet less formal way to document the end of life wishes for dementia patients and their families.

The ACP is not just a document but is the end product of a process of discussion between the patient and/or the family, usually guided by social and healthcare providers. It does not involve only life-sustaining treatment (LST) as in the AD, and is not a "refusal form" of specific types of care. The best thing about the ACP is that it allows even a cognitively impaired person to have a say about many issues preceding and even after his/her own death, although they may lack the mental capacity to formally make a will or an AD.

The following table summarizes the difference between AD and ACP:

Advance Care Planning **預立醫囑/預立醫療自主計劃**	**Advance Directive** **預設醫療指示**
A process of discussion and statements of personal wishes regarding future end of life care	A written document
Can be made by proxies and cognitively impaired persons	Only made by mentally capable adults
Not legally binding	Legally binding in many regions
Does not require medical ascertainment of mental capacity; can be witnessed by family	Requires assessment of mental capacity by a doctor and formal witnessing procedure by others not related to the individual
Contains views, lifestyle choices and preferences of daily care, in addition to life-sustaining therapies	A refusal of life-sustaining therapies including artificial nutrition and hydration
Immediately becomes a reference for present and future care	Only becomes valid when the person loses mental capacity or consciousness
Suggested to be regularly reviewed and updated	Need to be voided and a new one made if decisions are revoked

As major neurocognitive disorder is an incurable condition, it is advisable for social and healthcare professionals to bring this matter to the attention of the patient and his/her caregivers, so that the former's autonomy can be exercised through the clear documentation of his/her wishes, in relation to his/her end of life period.

More information and samples of ACPs can be obtained from the following websites:

1. The 5 Wishes (English)
   https://www.fivewishes.org/for-myself/
2. Peace of Mind booklet (Chinese)
   http://www.ioa.cuhk.edu.hk/end-of-life-care/wp-content/uploads/2020/10/booklet_2.pdf
3. About End of Life Care (Chinese and English)
   https://www.jccpa.org.hk/tc/facts_on_dementia/caring_tips/advance_care_planning/index.html

6.3 Enduring Power of Attorney, Guardianship Order and Advance Directive

6.3.1 Enduring Powers of Attorney (EPA) for Financial Management Only

Like most common law jurisdictions, Hong Kong SAR has put in place the Enduring Power of Attorney Ordinance, Cap. 501 since 1997. This is an advance instrument by a maker to appoint another person of the maker's choice, while still mentally capable, to manage those areas of financial affairs specified therein, in the event that the maker subsequently loses mental capacity to take charge of finances. EPA must be in prescribed form. Due to extremely low take-up (only 54 EPA registered as at 30 June 2012), two important consultations were completed by the Law Reform Commission to improve the system respectively in April 2007 (Report in March 2008) and in July 2009 (Report in July 2011). The first mentioned consultation dealt with the cumbersome dual-witness requirement (i.e. simultaneous witnessing by a lawyer and a medical doctor) and the second one dealt with expanding the scope of EPA to include personal and health care and new supervisory powers to Guardianship Board. The first law amendment was made effective on 3 July 2012 to relax dual-witness requirement to one witness following by the other within 28 days. The second law amendment is now being actively processed and a draft bill known as Continuous Power of Attorney Ordinance was open for public consultation on 28 December 2017.

Therefore, those older adults at risk of or in the very early stage of neurocognitive disorder should be advised and encouraged to make such an advance instrument at the time while s/he is still mentally capable to appoint his/her surrogate.

6.3.2 Guardianship Order (GO)

Hong Kong's adult guardianship system has established in February 1999. Guardianship Board will, on application, appoint a guardian for a patient or a mental handicap (who must be over 18 years) if certain legal criteria are satisfied. These criteria include whether the patient (i.e. subject-person) is established by medical evidence that s/he is a mentally incapacitated person within the meaning of s.2 of Mental Health Ordinance Cap. 136. Also, it must be proved that the subject-person is suffering from mental incapacity to an extent or degree that warrants his/her reception into guardianship. The Board also considers if there are other informal means through which the particular need of the subject-person can be satisfied without guardianship. The Board aims to act as a facilitator and empowering authority to protect or promote the best interests of the subject-person. It is important to mention that a person died during guardianship will need to be put under a coroner's inquest. Also, all guardianship orders will have to be reviewed before expiration. Currently, the Board deals with around 600 matters a year and predominant users are elderly people.

The Guardianship Board can grant to a guardian six powers which include consent to treatment (but not refusal or withdrawal of treatment), to decide on finance and residence arrangement. Unlike EPA, the financial power of a guardian is restricted to the use of cash or savings within a monthly limit according to the latest median monthly earnings (currently HK$12,500). Therefore, if the assets are sizeable and varied, the family should apply to High Court under Part II of the Mental Health Ordinance for a committee appointment. With regard to medical treatment to be provided to a mentally incapacitated person, a clinician can provide treatment without consent of a legal guardian provided such treatment is in the person's best interests pursuant to Part IVC of the Mental Health Ordinance. In Hospital Authority practice, two medical practitioners are required to sign for the medical procedure. It is good clinical management to seek the agreement (not consent) of the next of kin at the same time. Mostly, no guardianship application is needed. Guardianship application is required only in controversial circumstances e.g. the treatment risk and benefit balance is not definitive or the patient or family objects to a treatment despite obvious medical benefits.

6.3.3 Advance Directive (AD)

In general and in Hong Kong context, advance directive is made by an adult while mentally capable to refuse certain specified life-sustaining treatments (LST) to be provided to him/her at a time when s/he becomes mentally incapacitated due to terminal illness, persistent vegetative state or irreversible coma. LST includes cardiopulmonary resuscitation and artificial hydration and nutrition, etc. Forms of AD are NOT prescribed by law in Hong Kong. However, the model form proposed by Law Reform Commission and the form used by Hospital Authority each sets out that the signing by the maker is in the presence of two witnesses, one of whom must be a medical practitioner. On 24 July 2020, the Food and Health Bureau published a report on end of life care in which inter alia proposal will be made towards promulgating a new law to provide for general principles of AD but will not prescribed a statutory form or set up a central registry.

In summary, EPA and AD can be made at the time when an adult is mentally capable whereas GO is used to promote the interests of a mentally incapacitated persons without having made any advance instruments. EPA can only be used to manage finance currently but is now being reviewed to expand the scope to personal care and medical decisions. On the other hand, AD takes charge of withholding or withdrawal of LST of patients in terminal conditions. Guardianship Board can only grant six limited powers to a guardian but the finance power remains restricted. Clinicians taking care of demented patients should have some understanding about the varied functions and purposes of the three legal provisions above.

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