

DIAGNOSING AND TREATING ALZHEIMER'S DISEASE

by

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DSM-IV DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DISEASE

Diagnostic criteria for Alzheimer's disease require the presence of:

- memory deficit that can be demonstrated objectively on cognitive testing;
- at least one other cognitive deficit such as:
 - ◆ **aphasia** (abnormal speech)
 - ◆ **executive function impairment** (difficulty with planning, judgment, mental flexibility, abstraction, problem-solving, etc.)
 - ◆ **agnosia** (recognition of people or objects), or
 - ◆ **apraxia** (performance of learned motor skills)
- together, these cognitive deficits must result in impairment in performance of daily activities
- these deficits must represent a decline from a previous higher level of functioning
- there must be no other neurological disease to account for the deficits

OTHER CONSIDERATIONS IN DIAGNOSING ALZHEIMER'S DISEASE

- Alzheimer's disease is by far the most common of the dementias.
- Alzheimer's disease pathology is often mixed with other dementia-related pathology such as cerebrovascular disease and Lewy bodies.
- Onset is gradual and progressive and new learning (short-term memory) is often affected first.
- The patient is often less aware of cognitive deficits than those around them.
- Alarm features that might cause the clinician to question this diagnosis include younger age (< 65 years), more abrupt onset, rapid progression, the presence of neurological signs in early disease, etc.

1. DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE: DELIRIUM

The hallmarks of delirium are:

- The confusion has an acute onset (hours to days).
- Attention is impaired. Reduced ability to focus, sustain, or shift attention.
- Evidence of a physiological cause such as medication effects, sepsis, metabolic abnormalities, etc.

Delirium can be:

- Hyperactive (agitated), e.g. alcohol withdrawal.
- Hypoactive ("pleasantly confused").

The **Confusion Assessment Method (CAM)** is a useful tool for identifying delirium.

1. Is there evidence of an acute change in mental status from baseline? Does mentation fluctuate through day?
2. Does the patient have difficulty focusing attention, e.g. being easily distractible, or keeping track of what is being said?
3. Is the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
4. Is there an altered level of consciousness? Not alert? Lethargic? Hypervigilant? Stuporous?

Delirium is suspected when (1) and (2), plus either (3) or (4) are present.

Another useful tool for identifying the impaired attention of delirium is to have the patient recite the months of the year in reverse order.

DIAGNOSTIC TIP: *Early or incipient dementia will render an individual more susceptible to developing delirium. If delirium is identified and resolves with treatment, such individuals should be followed for subsequent development of a dementia.*

2. DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE: DEPRESSION

Early Alzheimer's disease and depression may have features in common which can cause diagnostic confusion, such as:

- declining self-care such as maintenance of hygiene, dress, grooming
- weight loss (although Alzheimer's disease patients usually eat well when food is prepared for them)
- social withdrawal
- psychomotor retardation, apathy, loss of motivation

Features that suggest depression include:

- an element of sadness or melancholy, tearfulness
- feelings of guilt, self-recrimination, worthlessness, hopelessness
- delusions that are mood-congruent, e.g. diseased, despicable, deserving of punishment
- somatic preoccupation

Tools for identifying depression:

- Geriatric Depression Scale: On the GDS-15 a score of 5 - 9 is suggestive of depression; a score of 10 or greater is strongly suggestive of depression
- SIG:E-CAPS mnemonic:

S	Sleep
I	Interest
G	Guilt
E	Energy
C	Concentration
A	Appetite
P	Psychomotor retardation
S	Suicidal thinking

DIAGNOSTIC TIP: *Late-life depression (especially first episode in late life) can be a harbinger of early dementia. It is appropriate to retest the patient for cognitive impairment after successful treatment for their depression.*

3. DIFFERENTIAL DIAGNOSIS OF AD: OTHER DEMENTIAS

(a) VASCULAR DEMENTIA (VaD)

The NINDS-AIREN diagnostic criteria for vascular dementia are:

1. *Dementia* defined by cognitive decline from a previously higher level of functioning manifested by impairment of memory and of impairment in at least one other cognitive domain. Deficits should be severe enough to interfere with activities of daily living not due to the physical effects of stroke alone.
2. *Cerebrovascular disease* defined by the presence of focal signs on neurologic exam consistent with stroke (with or without history of stroke) AND evidence of relevant CVD by brain imaging (CT or MRI)...
3. *A relationship between the above two disorders* manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or (c) fluctuating, stepwise progression of cognitive deficits.
4. Clinical features consistent with the diagnosis of probably vascular dementia include:
 - early presence of gait disturbance;
 - history of unsteadiness and frequent, unprovoked falls;
 - early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease;
 - pseudobulbar palsy;
 - personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive functions.

DIAGNOSTIC TIP: *Pure VaD is relatively uncommon. AD exacerbated by cerebrovascular lesions is more common. When a dementia presents like AD (gradual onset and progression) but evidence of ischemic lesions is found on examination, the likely diagnosis is AD with comorbid cerebrovascular disease rather than pure VaD.*

(b) DEMENTIA WITH LEWY BODIES (DLB)

Diagnostic criteria for a diagnosis of Dementia with Lewy Bodies according to the International Consensus Consortium (McKeith et al 1996) are:

1. Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually

evident with progression. Deficits on tests of attention and frontal-subcortical skills and visuospatial ability may be especially prominent.

2. Two of the following are required for a diagnosis of probable DLB:
 - fluctuating cognition with pronounced variations in attention and alertness
 - recurrent visual hallucinations which are typically well-formed and detailed
 - spontaneous motor features of Parkinsonism
3. Features supportive of the diagnosis are:
 - repeated falls
 - syncope or transient loss of consciousness
 - neuroleptic sensitivity
 - systematized delusions
 - hallucinations in other modalities

DIAGNOSTIC TIPS:

- ◆ *DLB and Alzheimer's disease neuropathology commonly coexist with resulting clinical expression on a spectrum from pure Alzheimer's disease to pure DLB.*
- ◆ *Patients with longstanding Parkinson's disease who develop dementia should not be diagnosed with DLB but rather with Parkinson's disease dementia (PDD) or Alzheimer's disease depending on the clinical features. The Parkinsonism of DLB should not be present for more than 12 months before the cognitive changes*

(c) **FRONTOTEMPORAL DEMENTIA**

The Lund-Manchester diagnostic criteria for frontotemporal dementia require all of the following core components to be present:

- (a) insidious onset and gradual progression
- (b) early decline in social interpersonal conduct
- (c) early impairment in regulation of personal conduct
- (d) early emotional blunting
- (e) early loss of insight

Supportive diagnostic features include:

- (a) behavioral disorder
- (b) decline in personal hygiene and grooming
 - mental rigidity and inflexibility
 - distractibility and impersistence
 - hyperorality and dietary change
 - utilization behavior
- (c) Speech and language:

- altered speech output (spontaneity and economy/press of speech)
- stereotypy of speech
- echolalia, perseveration, mutism

(d) Physical signs:

- primitive reflexes
- incontinence
- akinesia
- rigidity
- tremor
- low/labile blood pressure.

(e) Investigations:

- neuropsychology: impaired frontal lobe tests; no amnesia or perceptual deficits
- EEG: normal on conventional EEG despite clinically-evident dementia
- brain imaging: predominant frontal and/or anterior temporal abnormality

DIAGNOSTIC TIPS:

- ◆ *Frontotemporal dementia commonly presents in middle-aged individuals*
- ◆ *Often presents to psychiatrists more than neurologists or geriatricians because of prominent behavioural and personality problems*
- ◆ *Memory impairment may be minor*

(d) **NORMAL PRESSURE HYDROCEPHALUS (NPH)**

The usual triad of symptoms is:

- cognitive impairment
- gait problems
- urinary incontinence

Plus – imaging evidence of hydrocephalus beyond the ex-vacuo hydrocephalus of atrophy.

(e) **OTHER DEMENTIAS**

A non-exhaustive list of other dementias includes:

- dementia of alcoholism (substance-induced persisting dementia)
- dementia of Parkinson's Disease
- HIV dementia
- dementia due to hypoxic encephalopathy
- dementia due to traumatic brain injury
- dementia due to various neurodegenerative diseases, e.g. multiple sclerosis, Huntington's disease, Progressive Supranuclear Palsy, etc.
- neurosyphilis
- Creutzfeldt-Jacob disease and variant CJD

4. INFORMATION TO SEEK IN THE HISTORY

(a) **INFORMATION RELATED TO FORGETFULNESS**

Enquire about forgetfulness (to the point of disability):

- forgets appointments, medications, bill payment, PIN numbers
- forgets recent events, e.g. having been places
- gets lost easily – at the mall, or driving
- loses car in parking lot
- cooking trouble: leaves stove on, leaves ingredients out of recipe
- misplaces things

(b) **INFORMATION RELATED TO EXECUTIVE FUNCTION**

- performance at work
- difficulty driving
- difficulty with games of skill, e.g. board and card games
- difficulty cooking for large group
- difficulty organizing finances
- cannot understand abstraction or humour (concreteness)
- difficulty operating appliances, tools, computers, TV remote, etc.
- withdrawal from social involvement
- diminishing self-care – dress, grooming, and hygiene
- ability to travel unescorted

(c) **INFORMATION RELATED TO OTHER COGNITIVE FUNCTIONS**

- trouble finding words and expressing oneself (aphasia)
- trouble tying shoes, getting dressed, playing an instrument, typing (apraxia)
- trouble recognizing familiar people or objects (agnosia)

DIAGNOSTIC TIP: *Apraxia and agnosia are uncommon in early-stage AD.*

(d) **OTHER IMPORTANT BACKGROUND AND CONTEXTUAL INFORMATION**

- history of presenting illness: onset and course, presence of hallucinations or delusions, presence of marked fluctuation in cognition, etc.
- past medical history: vascular disease (stroke, heart attack, CABG, PAD), liver disease, uremia, thyroid disorders, syphilis, HIV, brain injury, etc.
- systems review: sleep apnea, depression, gait problems/falls, urinary incontinence
- personal/social history: substance abuse, educational/occupational attainment, literacy

DIAGNOSTIC TIP: *obtaining collateral history from a reliable informant is of tantamount importance. Is the informant more or less concerned about the deficits than the patient? As an indicator of disability, ask the informant if he/she feels the patient could live entirely unsupported in the community?*

5. PHYSICAL EXAMINATION FINDINGS TO SEEK

- nutritional status
- thyroid signs
- signs of respiratory failure
- signs of hepatic failure
- detailed neurological examination
- observations about mental status: appearance, behaviour, speech

6. LABORATORY AND IMAGING WORK-UP

The basic laboratory work-up should include:

- CBC
- glucose
- electrolytes, creatinine.
- serum calcium
- TSH
- B12

Other tests may be necessary depending on the context, e.g.:

- blood gases, oximetry, sleep apnea screening.
- serum folate.
- liver function tests and serum ammonia.
- syphilis serology.
- drug levels, e.g. digoxin.

Brain imaging is not recommended in all cases but should be considered when:

- onset is at a younger age (< 65 years).
- onset is sudden
- progression is rapid
- vascular dementia is suspected
- abnormal neurological signs are present
- the patient is on anticoagulants or has bleeding disorder
- recent head injury
- Normal Pressure Hydrocephalus is suspected

7. COGNITIVE TESTING: PERFORMING THE STANDARDIZED MINI-MENTAL STATE EXAM

The Mini-Mental State Exam (MMSE) was described by Folstein, Folstein, and McHugh in 1975 (Folstein MF, Folstein SE, and McHugh PR J Psychiatr Research 1975;12:189-198) and is the most commonly used cognitive test used to assess patients with dementia. The original description of the test unfortunately lacked specific instructions on how the test should be administered, which has led to great variations in scoring for the test. Dr.D.W.Molloy has described a “Standardized Mini-Mental State Exam” which has given very precise instructions for administering the MMSE. The following is a summary of the instructions for using the SMMSE.

Test item	How to frame the question	Requirements
Introduction	Introduce the test with some non-threatening explanation such as: “I am going to give you a standardized test of your memory. Please don’t be insulted if you find some of the questions very simple”. Give positive affirmation after the patient’s answers, even when wrong, e.g. “Well done”.	
Orientation to date <ul style="list-style-type: none"> • Year • Season • Month • Date • Day of week 	“What year is it?” “What season is it?” “What month is it?” “What date is it?” “What day of the week is it?”	Allow self-corrections. Allow 10 seconds for each reply. Answers must be exact except for the season (may be out by one week from the official start of the season; and the date (may be out by one day).
Orientation to place <ul style="list-style-type: none"> • Country • Province • City • Building (street address of home) • Floor (room in house) 	“What country are we in?” “What province are we in?” “What city/town are we in?” “What is the name of this building?” (If in the patient’s own home, ask for the street address). “What floor are we on?” (If in the patient’s home, ask “What room are we in?”	Allow 10 seconds for each answer. Accept exact answers only.

Registration of 3 words	<p>"I am going to name three objects. After I have said all three objects, I want you to repeat them. Remember what they are, because I am going to ask you to name them again in a few minutes." Say them slowly at approximately 1 second intervals. Examples: ball/car/man; apple/penny/table.</p>	<p>Score 1 point for each object spontaneously recalled within 20 seconds. If the patient has not registered all 3 words, repeat the words up to 5 times until the words have registered (but do not change the score).</p>
WORLD	<p>"Spell the word WORLD (as in the world we live in)"</p> <p>"Now spell WORLD backwards."</p> <p>On the original MMSE test, Folstein et al offered us the choice of using either WORLD or serial 7's. Serial 7's are discouraged except under the rare circumstance that WORLD is not possible for the patient but serial 7's are.</p>	<p>You may assist the patient to spell WORLD forwards if they are not certain how. Allow 30 seconds. Allow self correction. If the patient says "I can't", you can encourage them to try anyway. Scoring WORLD has been the source of much confusion. Give 1 point for each letter in the <i>correct relative sequence</i>. Correct answer is DLROW. If the patient gave a partial answer of DLO, DRO, or DRW, all would score 3 because the letters are in the correct sequence relative to one another. If the patient responded DLORW, score 4 because if you eliminate either the O or the R, everything left is in the correct relative sequence.</p>
Naming	<p>Show the patient a wristwatch and ask "What is this called?" Show the patient a pencil and ask "What is this called?"</p>	<p>Allow 10 seconds for each reply. Clock is not acceptable for watch; and pen is not acceptable for pencil.</p>
No ifs, ands, or buts.	<p>"Please repeat this phrase after me: No ifs, ands, or buts."</p>	<p>Allow 10 seconds. Response must be exact including the S's on ifs, ands, and buts.</p>
Close your eyes	<p>Show the patient the written words: Close your eyes. Then say "Read these instructions and then do what it says".</p>	<p>Allow 10 seconds. Score 1 point if the patient closes his/her eyes. You may repeat the instructions up to 3 times.</p>

Write a sentence	Give the patient a piece of paper and a pencil. Instruct the patient: "Write any complete sentence on that piece of paper."	Allow 30 seconds. Score 1 point for any sentence that is a grammatically complete sentence. For instance "How are you?" is acceptable but "John Doe" is not. Ignore spelling mistakes or faulty punctuation.
Pentagons	Show the patient the intersecting pentagons and ask the patient to copy the diagram on a piece of paper.	Allow one minute. Allow use of eraser and self-correction. Score 1 point if the patient draws two pentagons intersecting with a 4-sided enclosure. Although not mentioned by Molloy, it is customary to require the pentagons to be roughly equal-sided (i.e. longest side not > 2 x shortest side).
3-stage command	Having previously ascertained which is the patient's NON-dominant hand, give instructions such as: "Listen to the following instructions but don't do anything until you have heard all the instructions. Take this piece of paper in your left/right (non-dominant) hand, then using two hands fold it in half, then place it on the floor."	Allow 30 seconds. Both hands should be free of encumbrances. Place the paper directly in front of them. Don't thrust it towards the patient. Patient must not fold the paper more than once.

8. OTHER COGNITIVE TESTS

- (a) **Clock Drawing Test.** The clock drawing test (CDT) is a common addition to the sMMSE in assessing cognition. The CDT draws on a number of cognitive domains such as working memory and executive functions (planning, conceptualizing, and visuoconstructional skills). The CDT is less affected by language, culture, and education than many other cognitive tests. A number of formal protocols with scoring systems have been proposed for the CDT; however most clinicians administer the test in an informal and subjective manner. The patient is usually presented with a circle of about 10 cm diameter drawn on paper. The examiner asks the patient to place the numbers around the circle like a clock; then the patient is asked to place hands on the clock at 10 minutes past 11 o'clock.
- (b) **The Montreal Cognitive Assessment (MoCA).** This test is available on line at www.mocatest.org. It is believed to be more sensitive for demonstrating early cognitive decline such as Mild Cognitive Impairment.

9. STAGING OF ALZHEIMER'S DISEASE: GLOBAL DETERIORATION SCALE (GDS)

Alzheimer's disease is a progressive neurodegenerative disorder that can be staged using a system devised by Reisberg, Ferris, deLeon, and Crook (Am J Psychiatry 1982 139:1136). The initial diagnosis of Alzheimer's disease is generally made in Stage 4. Stage 3 roughly coincides with what is now called Mild Cognitive Impairment.

GLOBAL DETERIORATION SCALE

Stage	Deficits in cognition and function	Usual care setting	Mean MMSE
1	Subjectively and objectively normal	Independent	29-30
2	Subjective complaints of mild memory loss. Objectively normal on testing. No functional deficit	Independent	29
3	Mild Cognitive Impairment (MCI) Earliest clear-cut deficits. Functionally normal but co-workers may be aware of declining work performance. Objective deficits on testing. Denial may appear.	Independent	25
4	Early dementia Clear-cut deficits on careful clinical interview. Difficulty performing complex tasks, e.g. handling finances, travelling. Denial is common. Withdrawal from challenging situations.	Might live independently – perhaps with assistance from family or caregivers.	20
5	Moderate dementia Can no longer survive without some assistance. Unable to recall major relevant aspects of their current lives, e.g. an address or telephone number of many years, names of grandchildren, etc. Some disorientation to date, day of week, season, or to place. They require no assistance with toileting, eating, or dressing but may need help choosing appropriate clothing.	At home with live-in family member. In seniors' residence with home support. Possibly in facility care, especially if behavioural problems or comorbid physical disabilities.	14
6	Moderately severe dementia May occasionally forget name of spouse. Largely unaware of recent experiences and events in their lives. Will require assistance with basic ADLs. May be incontinent of urine. Behavioural and psychological symptoms of dementia (BPSD) are common, e.g. delusions, repetitive behaviours, agitation.	Most often in Complex Care facility.	5
7	Severe dementia Verbal abilities are lost over the course of this stage. Incontinent. Needs assistance with feeding. Loses ability to walk.	Complex Care	0

10. NON-PHARMACOLOGIC MANAGEMENT OF ALZHEIMER'S DISEASE

The following are some general measures to consider in the support of community-dwelling patients with Alzheimer's disease:

- meal support such as Meals on Wheels, especially for those living alone (monitor patient's weight)
- consider kitchen safety: fire hazard, food freshness, etc.
- consider medication supervision through Home Care. Blistercards?
- bathing - does the patient need a bathing assistant or bath program?
- wandering - consider a Safely Home bracelet (Alzheimer's Society)
- socialization - consider an adult day centre
- be vigilant for signs of financial or other elder abuse, self-neglect, etc.
- establish a chronic disease management approach to following the patient with Alzheimer's disease, e.g. using a flow sheet and planned visits
- assess driving safety

11. CHOLINESTERASE INHIBITOR THERAPY: CONTRAINDICATIONS AND ADVERSE REACTIONS

(a) Relative contraindications to cholinesterase therapy

- severe hepatic or renal disease
- significant bradycardia or AV block
- significant bronchospastic disease
- obstructive urinary disease
- active peptic ulcer disease
- seizure disorder

(b) Most common side effects

- nausea and vomiting are most common.
- anorexia and weight loss
- diarrhea
- disturbing dreams (especially donepezil)
- muscle/leg cramps
- syncope or dizziness

(c) Drug interactions:

- donepezil and galantamine are metabolized through the CYP450 enzyme system
- toxicity may therefore be increased by concomitant use of certain CYP450 inhibitors, e.g. paroxetine, erythromycin, prednisone, grapefruit juice, nefazodone)
- effectiveness of donepezil and galantamine may be decreased by CYP450 inducers such as carbamazepine, phenytoin, and rifampin
- concomitant use of anticholinergic drugs may reduce the efficacy of cholinesterase inhibitors, e.g. tricyclic antidepressants, oxybutinin, etc.

12. CHOLINESTERASE INHIBITOR THERAPY: DOSE TITRATION

Drug	Starting dose	Titration period	Dose increase per titration period	Usual effective dose
Donepezil	5 mg once/day*	4-6 wks	5 mg/day	10 mg once/daily
Galantamine	8 mg ER once/day	4-6 wks	8 mg/day	16-24 mg once daily
Rivastigmine	1.5 mg twice daily	2-4 weeks	1.5 mg twice daily	3-6 mg twice daily

**For the very frail or those who have had previous adverse effects to other cholinesterase inhibitors, consider starting at a lower dose of donepezil 2.5 mg once daily*

13. CHOLINESTERASE INHIBITOR THERAPY: SWITCHING

There are two possible reasons for switching cholinesterase inhibitors:

1. current cholinesterase inhibitor is poorly-tolerated despite slower titration
2. current cholinesterase inhibitor is deemed ineffective

Choose the protocol below depending on the reason for switching.

Switching for poor tolerability

- stop the current cholinesterase inhibitor
- washout period of 2 days for galantamine and rivastigmine, or 5-7 days for donepezil.
- start the new cholinesterase inhibitor using the same titration schedule as for new starts.

Switching for lack of efficacy. The following protocol is proposed:

CURRENT DRUG to be TAPERED OFF DUE TO <u>LACK OF EFFICACY</u>				
	Current Dose (Total mg/d)	Dose End of Wk 1	Dose End of Wk 2	Maximum Dose**
Donepezil	10	5	0	
	5	2.5	0	
	2.5	0	0	
Galantamine	24	16	0	
	16	8	0	
	8	0	0	
Rivastigmine (>1.5mg/d split into bid dosing if possible)	12	6	0	
	9	4.5	0	
	6	3	0	
	3	1.5	0	
NEW DRUG TO BE ADDED WHILE CURRENT DRUG TAPERED				
Donepezil or	-	2.5-5	5	10
Galantamine or	-	8	16	24
Rivastigmine	-	1.5-3	3-6	6-12

14. CHOLINESTERASE INHIBITOR THERAPY: DISCONTINUING THERAPY

As a group, the cholinesterase inhibitors are at best modestly effective. The principal attraction of the cholinesterase inhibitors is to help the patient maintain functional autonomy in the early stages of Alzheimer's disease. The clinician may decide to discontinue therapy under a number of circumstances:

- patient is now institutionalized and has lost functional autonomy
- patient has so much comorbid illness that some small improvement in Alzheimer's disease-related issues may have no impact on the patient's overall condition
- drug may be contributing to symptoms such as anorexia, weight loss, nausea, muscle cramps, etc.

There is evidence that the accrued benefits of taking cholinesterase inhibitors may be lost and never regained if therapy is suspended for 4-6 weeks. Therefore, if the cholinesterase inhibitor is discontinued and a noticeable deterioration in the patient's Alzheimer's disease status is observed, consider restarting therapy before this window of time closes.

Also when discontinuing therapy, be aware that cholinesterase inhibitors may also suppress the emergence of various behavioral symptoms such as agitation, hallucinations, and delusions. Watch for an increase in such symptoms and consider restarting the drug if it appears that it has been stabilizing the patient's behavior.

15. LINKS

GPAC Guidelines for Cognitive Impairment in the Elderly – Recognition, Diagnosis and Management [<http://www.health.gov.bc.ca/gpac/pdf/cognitive.pdf>]