NEUROCOGNITIVE DISORDERS

Major Neurocognitive Disorder Due to Alzheimer's Disease

MNCD

DSM-5-TR 294.1X | ICD-10-CM G30.9 WITH F02.80 / F02.81

Progressive amnestic dementia of insidious onset, driven by amyloid plaques and tau tangles, ending in total functional dependence.

PREVALENCE AGE 65+	TYPICAL ONSET	SEX RATIO	COURSE
~11% of US adults 65+	After 65; <65 is early-onset	~2:1 female:male cases	8-10 yr median from dx

CLINICAL PICTURE

- Episodic memory fails first, with repeated questions, misplaced objects, growing reliance on notes and family, and rapid forgetting of recent conversations.
- Word-finding pauses, semantic paraphasias, and impoverished conversation follow, alongside visuospatial errors and getting lost on familiar routes.
- Executive decline appears as poor financial judgment, missed bills, unsafe driving, and vulnerability to scams long before basic self-care is lost.
- Insight is limited and often absent, so families rather than patients report the decline while patients minimize or confabulate around the gaps.
- Neuropsychiatric symptoms affect up to 90% over the course: apathy earliest, then depression, agitation, delusions of theft, and evening sundowning.
- Function declines in a predictable order, from instrumental tasks such as cooking and medications down to dressing, feeding, and continence.

DIAGNOSTIC CRITERIA AT A GLANCE

- Major neurocognitive disorder requires significant decline in one or more cognitive domains, established by informant report plus objective standardized testing.
- The deficits interfere with independence in everyday activities, meaning the person needs assistance with tasks such as paying bills or managing medications.
- Deficits do not occur exclusively during an episode of delirium and are not better explained by another mental disorder such as major depression.
- Probable Alzheimer's requires a causative genetic mutation, or all of clear memory decline, steady gradual progression, and no evidence of mixed etiology.
- Specify with or without behavioral disturbance and rate severity as mild, moderate, or severe according to the level of daily assistance required.

NEUROBIOLOGY & PHYSIOLOGY

- Extracellular amyloid-beta plaques and intracellular hyperphosphorylated tau tangles spread outward from entorhinal cortex and hippocampus along Braak stages.
- Cholinergic neuron loss in the nucleus basalis of Meynert underlies the memory deficit and provides the rationale for cholinesterase inhibitor therapy.
- APOE e4 raises risk roughly 3-fold with one allele and 8-12 fold with two, while APP, PSEN1, and PSEN2 mutations cause autosomal dominant early-onset disease.
- CSF and plasma biomarkers show low amyloid-beta 42 with elevated phosphorylated tau 181 or 217, and amyloid or tau PET confirms pathology in living patients.
- MRI shows medial temporal and hippocampal atrophy, and FDG-PET shows temporoparietal and posterior cingulate hypometabolism with sparing of primary cortex.
- Modifiable risks including hypertension, diabetes, obesity, smoking, hearing loss, depression, and low education account for roughly 40% of population risk.

PSYCHOLOGICAL MECHANISMS

- Excess disability arises when caregivers over-assist or environments overwhelm, producing more observed impairment than the underlying pathology dictates.
- Agitation is usually communication of unmet need, whether pain, boredom, fear, or overstimulation, and responds to antecedent-based behavioral analysis.
- Preserved procedural and emotional memory allows habit routines, familiar music, and demonstration to work when explicit verbal instruction fails.
- Catastrophic reactions follow demands that exceed residual capacity, so simplifying tasks and reducing the number of choices reliably restores calm.
- Caregiver depression affects 30-40%, and measured caregiver burden predicts nursing home placement more strongly than the patient's cognitive score.

DIFFERENTIAL & COMORBIDITY

- Distinguish from delirium by the acute onset, fluctuating attention, and identifiable medical trigger, remembering that the two conditions frequently coexist.
- Vascular disease shows stepwise decline with infarcts, while Lewy body disease brings visual hallucinations, parkinsonism, REM sleep behavior disorder, and fluctuation.
- Frontotemporal dementia usually presents before age 65 with disinhibition, apathy, or progressive language loss, with episodic memory relatively spared early.
- Screen reversible contributors including B12 deficiency, hypothyroidism, normal pressure hydrocephalus, subdural hematoma, and total anticholinergic burden.
- Depression can mimic dementia with poor effort and do-not-know answers, and it also commonly coexists, so an adequate antidepressant trial is warranted.

Treatment EVIDENCE-BASED MANAGEMENT

PHARMACOLOGIC

- **Donepezil 5-10 mg/day**, rivastigmine patch, or galantamine give modest symptomatic benefit; GI upset, bradycardia, and vivid dreams are common effects.
- **Memantine 10 mg twice daily** is added at moderate to severe stages as an NMDA antagonist, generally better tolerated than cholinesterase inhibitors.
- Anti-amyloid monoclonals **lecanemab** and donanemab modestly slow early-stage decline but require APOE genotyping and serial MRI monitoring for ARIA.
- Avoid antipsychotics where possible given the boxed warning for increased mortality in dementia; **brexpiprazole** is FDA-approved for agitation in Alzheimer's.
- Deprescribe anticholinergics, benzodiazepines, and sedative-hypnotics, which worsen cognition and fall risk far more than they improve behavior.

PSYCHOTHERAPY

- **Cognitive stimulation therapy**, delivered as 14 group sessions over 7 weeks, produces cognitive and quality-of-life gains rivaling cholinesterase inhibitors.
- **Reminiscence therapy** and structured life review improve mood, engagement, and communication in the mild to moderate stages of the illness.
- **Behavioral activation** and problem-solving therapy adapted for mild impairment treat comorbid depression without adding medication burden.
- **Caregiver skills training** such as the REACH II protocol reduces caregiver depression and measurably delays institutional placement.
- Person-centered communication training, meaning short sentences, one instruction at a time, and no quizzing, reduces resistance during personal care.

ADJUNCT & SUPPORTIVE

- Stage and track decline with the **MoCA** or **MMSE** plus a functional measure, repeating every 6-12 months to document the individual trajectory.
- Environmental measures matter: consistent routine, daylight exposure, labeled rooms, reduced clutter, and nighttime safeguards against wandering.
- Address driving, firearms, finances, and wandering explicitly and early, and complete advance directives and surrogate decision-making while capacity remains.
- Exercise, hearing aids, blood pressure control, and sustained social engagement slow functional decline and reduce neuropsychiatric symptom burden.
- Connect families to adult day programs, respite care, the Alzheimer's Association helpline, and palliative or hospice services in the late stages.

CLINICAL PEARLS

- The informant, not the patient, provides the diagnostic history.
- Any acute change in a dementia patient is delirium until proven otherwise.
- Behavior is communication: look for pain, infection, or overstimulation first.

References

American Psychiatric Association. (2016). *The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia*. American Psychiatric Association Publishing. https://doi.org/10.1176/appi.books.9780890426807

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.). https://doi.org/10.1176/appi.books.9780890425787

Boland, R., Verduin, M. L., & Ruiz, P. (2021). *Kaplan & Sadock's synopsis of psychiatry* (12th ed.). Wolters Kluwer.

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimaki, M., Larson, E. B., Ogunniyi, A., ... Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, 396(10248), 413-446. https://doi.org/10.1016/S0140-6736(20)30367-6

National Institute on Aging. (n.d.). *Alzheimer's disease fact sheet*. U.S. Department of Health and Human Services. https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet

Stahl, S. M. (2021). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (5th ed.). Cambridge University Press.

van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L. D., & Iwatsubo, T. (2023). Lecanemab in early Alzheimer's disease. *The New England Journal of Medicine*, 388(1), 9-21. https://doi.org/10.1056/NEJMoa2212948

NOTE

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