W H I T E P A P E R

Organic Brain Syndrome

The Dementias

Alzheimer's · Lewy Body · Vascular · Frontotemporal · Mixed

A Complete Guide for Patients, Families, and Caregivers

Diagnosis · Current Medications · Promising Clinical Trials · Caregiver Support

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Sources: Alzheimer's Association, Lewy Body Dementia Association, AFTD, NIA, NIH ClinicalTrials.gov, FDA

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1. EXECUTIVE SUMMARY

Organic Brain Syndrome (OBS) — the umbrella clinical term for the dementias — describes a group of progressive neurological diseases that destroy memory, judgment, language, and the ability to function independently. The term encompasses Alzheimer's disease (the most common form), Lewy Body Dementia, Vascular Dementia, Frontotemporal Dementia, Mixed Dementia, and several less common conditions. Together they represent the single largest cause of long-term care dependency in the United States.

As of 2026, an estimated 7.4 million Americans age 65 and older are living with clinical Alzheimer's dementia — and that figure represents only one slice of the broader dementia population. When all dementia types are counted, the United States has well over 10 million people living with some form of Organic Brain Syndrome, and the number is projected to nearly double by 2050.

Unlike many chronic diseases, the dementias erode the very capacity required to plan for them. Cognitive decline often outpaces awareness, and families discover that the financial, legal, and care decisions they meant to address can no longer be made by the patient. The window for protective planning closes quietly and early — sometimes years before a formal diagnosis.

This white paper gives patients, family members, and caregivers an honest, current picture of Organic Brain Syndrome — from the major disease types through advanced stages. It covers:

- What each form of dementia is and how it progresses
- How they are diagnosed and staged
- Every major current maintenance medication and what it does
- The most promising clinical trials underway in 2026 — including 2025 breakthroughs and setbacks
- How the caregiver journey typically unfolds and what caregivers need to know
- The critical importance of early planning — before cognition closes the door

2. UNDERSTANDING ORGANIC BRAIN SYNDROME

What Is Organic Brain Syndrome?

Organic Brain Syndrome is a clinical term used to describe physical (organic) disorders of the brain that cause progressive decline in cognitive function — memory, reasoning, language, judgment, and personality. It is distinguished from psychiatric or 'functional' conditions because it has identifiable biological causes: protein deposits, neuron death, blood vessel damage, or other structural pathology.

Today, clinicians more often use the term 'major neurocognitive disorder' (the DSM-5 designation) or simply 'dementia.' But the older term 'Organic Brain Syndrome' remains widely used in legal documents and elder-care planning because it captures the full range of conditions that cause cognitive dependency.

The Major Types of Dementia

Dementia is not a single disease. It is a category of diseases, each with distinct biology, symptoms, and progression. Most people in advanced stages have mixed pathology — more than one disease process occurring at the same time.

Alzheimer's Disease (AD) — 60–80% of all dementia cases

The most common form. Caused by the accumulation of two abnormal proteins in the brain: beta-amyloid (plaques) and tau (tangles). These deposits trigger neuron death starting in the hippocampus — the brain's memory center — and spread outward over years.

- **Early symptoms:** Difficulty remembering recent conversations, names, and appointments; misplacing items; mild disorientation in familiar settings.
- **Middle stage:** Communication problems, confusion about time and place, poor judgment, behavioral changes, getting lost.
- **Late stage:** Loss of speech, mobility, swallowing, and bladder/bowel control; full dependency.
- **Typical course:** 4–8 years from diagnosis to death, but can extend 20 years depending on age and overall health.

Lewy Body Dementia (LBD / DLB) — 5–10% (more when mixed)

Caused by abnormal deposits of alpha-synuclein protein (Lewy bodies) inside brain cells — the same protein involved in Parkinson's disease. Distinct from Alzheimer's in that it tends to affect attention, alertness, and visual processing before significantly impairing memory.

- **Distinguishing symptoms:** Vivid recurrent visual hallucinations; large fluctuations in alertness from hour to hour; REM sleep behavior disorder (acting out dreams); Parkinson-like motor symptoms; severe sensitivity to antipsychotic drugs.
- **Typical course:** 5–8 years; progresses faster than Alzheimer's once motor symptoms appear.

- **Critical caution:** Many antipsychotic medications can cause severe, sometimes fatal reactions in LBD patients. Diagnosis matters.

Vascular Dementia (VaD) — 5–10% pure; much higher as mixed

Caused by impaired blood flow to the brain — strokes, mini-strokes (TIAs), or chronic small-vessel disease. Brain tissue dies in the affected areas, and cognitive function declines.

- **Distinguishing symptoms:** Often appears 'stepwise' — sudden declines following vascular events, with relative stability between. Executive function (planning, judgment, organization) often affected before memory.
- **Risk factors:** High blood pressure, diabetes, high cholesterol, smoking, atrial fibrillation, prior strokes.
- **Typical course:** Highly variable; aggressive treatment of vascular risk factors may slow progression.

Frontotemporal Dementia (FTD) — ~3% overall; leading cause under age 65

A group of disorders affecting the frontal and temporal lobes of the brain. Often involves abnormal accumulation of tau or TDP-43 protein. Hits at younger ages — typically 45–65 — and frequently runs in families.

- **Two main types:** Behavioral variant (bvFTD) — dramatic personality and behavior changes; Primary progressive aphasia (PPA) — progressive loss of language.
- **Distinguishing symptoms:** Loss of empathy, social judgment, and inhibition; new compulsions; food preferences may change radically; memory often preserved early.
- **Typical course:** 7–13 years from onset; high genetic component (40% have a family history).

Mixed Dementia — extremely common at older ages

More than one disease process occurring simultaneously — most often Alzheimer's combined with Vascular Dementia, or Alzheimer's combined with Lewy Body Dementia. Autopsy studies show that the majority of people over 80 diagnosed with 'Alzheimer's' actually have mixed pathology.

Mixed dementia typically progresses faster than any single form and complicates treatment because medications targeting one pathway may not address the others.

Other Forms of Dementia

- **Creutzfeldt-Jakob Disease (CJD):** Rare prion disease; rapid progression over months; uniformly fatal.
- **Korsakoff Syndrome:** Caused by chronic thiamine deficiency, usually from long-term alcohol abuse. Severe memory impairment.
- **Normal Pressure Hydrocephalus (NPH):** Excess cerebrospinal fluid; classic triad of gait disturbance, cognitive impairment, and urinary incontinence. Potentially reversible with shunt surgery.

- **Huntington's Disease:** Inherited disorder causing movement, cognitive, and psychiatric symptoms; usually diagnosed 30–50.
- **HIV-Associated Dementia, traumatic brain injury (CTE), and dementia secondary to other chronic conditions.**

How Common Is Organic Brain Syndrome?

7.4 million Americans age 65+ living with Alzheimer's dementia in 2026

~200,000 Americans under age 65 with younger-onset Alzheimer's

1 in 9 Americans age 65+ has Alzheimer's dementia (11%)

64% of Americans with Alzheimer's are women

1 in 5 lifetime risk of Alzheimer's for a 45-year-old woman (1 in 10 for men)

13.8 million projected U.S. Alzheimer's cases by 2060, absent breakthroughs

5th-leading cause of death for Americans 65+ (Alzheimer's specifically)

What Causes Organic Brain Syndrome?

Each dementia has its own root cause, but several risk factors are common across all forms:

Age — The Single Largest Risk Factor

- Dementia risk doubles roughly every 5 years after age 65.
- By age 85, an estimated 33% of Americans have Alzheimer's or another dementia.

Genetics

- Early-onset familial Alzheimer's: caused by mutations in PSEN1, PSEN2, or APP genes — autosomal dominant, very rare.
- APOE ε4: the most important genetic risk factor for late-onset Alzheimer's. One copy roughly triples risk; two copies increase it ~8–12 times.
- FTD: 40% of patients have a family history; key genes include MAPT, GRN, and C9orf72.
- Huntington's: caused by a single dominant gene mutation; 50% chance of inheritance from an affected parent.

Cardiovascular and Lifestyle Risk Factors

- Untreated high blood pressure, especially in midlife
- Diabetes (Type 2)
- Obesity and physical inactivity
- Smoking
- Excessive alcohol use
- Untreated hearing loss
- Social isolation and depression
- Repeated head trauma (CTE)
- Air pollution exposure

> *The 2024 Lancet Commission on dementia prevention identified 14 modifiable risk factors that, taken together, could potentially prevent or delay nearly 45% of dementia cases worldwide. Source: Lancet Commission on dementia prevention, intervention, and care.*

Symptoms of Organic Brain Syndrome

Dementia symptoms vary by type, but all forms progressively impair function. Symptoms fall into two broad categories: cognitive (thinking) and behavioral/psychological (mood and behavior). Both worsen over time and eventually drive care needs.

Core Cognitive Symptoms

- Short-term memory loss — particularly early in Alzheimer's
- Executive dysfunction — trouble planning, organizing, problem-solving
- Language difficulty — word-finding, comprehension
- Disorientation in time and place
- Visuospatial problems — getting lost, trouble with depth perception
- Loss of recognition — eventually including family members
- Impaired judgment — financial decisions, safety awareness

Behavioral and Psychological Symptoms (BPSD)

- Depression and anxiety (occur in 40–60% of dementia patients)
- Apathy — often the earliest behavioral change
- Agitation and aggression — most common in middle-to-late stages
- Hallucinations (visual hallucinations are hallmark of Lewy Body Dementia)
- Delusions, especially paranoid (e.g., 'someone is stealing from me')
- Sleep disturbance, including sundowning (worsening confusion in late afternoon/evening)
- Wandering
- Repetitive behaviors and questions

> *Behavioral and psychological symptoms — not memory loss — are the most common reason families place a loved one in residential memory care. Sleeplessness, wandering, agitation, and aggression exhaust caregivers faster than memory decline alone.*

How Does Dementia Progress? The Seven Stages

The most widely used staging system for Alzheimer's disease and most other dementias is the Global Deterioration Scale (GDS), also called the Reisberg Scale. It divides cognitive decline into seven stages — from no impairment through profound dementia.

Stage	Description	Average Duration	Care Setting
Stage 1 — No Impairment	Normal function. No memory complaints. No clinical signs.	—	Independent
Stage 2 — Very Mild Decline	Normal forgetfulness associated with aging. Misplacing objects, forgetting names. Not detectable on exam.	Variable (years)	Independent
Stage 3 — Mild Decline / MCI	Mild Cognitive Impairment. Co-workers and family notice changes. Trouble remembering new names, recent reading. Anxiety begins.	2–7 years	Independent; early planning critical
Stage 4 — Moderate Decline / Early Dementia	Clear deficits on clinical interview. Difficulty with finances, complex tasks, recent events. Diagnosis usually made here.	2 years	Independent with help; daily check-ins
Stage 5 — Moderately Severe / Mid-Stage	Cannot survive without assistance. Disoriented to time and place. Help needed with clothing, hygiene reminders.	1.5 years	Daily home care or assisted living
Stage 6 — Severe Decline / Late-Mid Stage	Significant personality changes. Needs help with all ADLs — toileting, bathing, dressing. Incontinence begins. Sleep disturbance.	2.5 years	Memory care or full-time home care
Stage 7 — Very Severe / Late Stage	Loss of verbal abilities, mobility, swallowing.	1.5–2.5 years	Skilled nursing facility; hospice

Stage	Description	Average Duration	Care Setting
	Total dependency. Bedbound in final months.		

On average, a person lives 4–8 years after an Alzheimer's diagnosis, though some live 20 years. Lewy Body and Frontotemporal Dementia typically progress somewhat faster. Vascular Dementia varies widely depending on control of cardiovascular risk factors. A person who lives a full course will spend approximately 40% of that time in the severe stages — precisely when 24-hour care is required.

> *Most families cannot accurately predict how long the journey will be. Some patients remain in Stage 4 for many years; others progress to Stage 6 in 18 months. This uncertainty is why early financial planning — done while the patient still has capacity — is irreplaceable.*

3. DIAGNOSIS

Diagnosis of dementia involves three steps: confirming that cognitive decline has occurred (not normal aging), determining whether the cause is dementia (versus depression, medication side effects, or reversible conditions), and identifying the specific type of dementia. The most accurate diagnoses are made by neurologists or geriatric psychiatrists who specialize in cognitive disorders.

Diagnostic Steps

- **Medical history and physical exam:** Symptom timeline, medication review, family history, vascular risk factors.
- **Cognitive testing:** Brief in-office screens (MMSE, MoCA, Mini-Cog) followed by formal neuropsychological testing when results are ambiguous.
- **Blood tests:** Rule out reversible causes — vitamin B12 deficiency, thyroid disease, syphilis, HIV. As of 2025, blood-based biomarkers can also help confirm Alzheimer's pathology.
- **Brain imaging:** MRI or CT to evaluate atrophy, strokes, tumors, hydrocephalus; specialized scans (PET, DAT) for specific diagnoses.
- **Biomarker testing:** Cerebrospinal fluid analysis or blood tests for amyloid and tau, where appropriate.
- **Genetic testing:** Considered for early-onset cases, strong family history, or before initiating disease-modifying therapy.

Cognitive Assessments

- **MMSE (Mini-Mental State Examination):** Score out of 30. Brief, widely used. Less sensitive to mild impairment and to non-amnestic dementias like FTD.
- **MoCA (Montreal Cognitive Assessment):** Score out of 30. More sensitive to mild cognitive impairment and to executive dysfunction.
- **Mini-Cog:** 3-minute screen combining 3-word recall and clock drawing. Useful in primary care.
- **Neuropsychological testing:** Comprehensive 2–6 hour battery; gold standard for distinguishing dementia types and severity.

Brain Imaging

- **MRI:** Detects atrophy patterns specific to each dementia type — hippocampal in Alzheimer's, frontal/temporal in FTD, white-matter changes in Vascular.
- **CT:** Used when MRI is contraindicated; less detailed.
- **FDG-PET:** Shows brain metabolic activity. Reduced metabolism in temporal/parietal regions supports Alzheimer's; frontal in FTD.
- **Amyloid PET:** Detects beta-amyloid plaques directly. Required by some payers before initiating Leqembi or Kisunla.

- **Tau PET:** Detects tau tangles. Increasingly used to confirm Alzheimer's pathology and stage disease.
- **DAT scan / I-MIBG cardiac scintigraphy:** Detects dopamine deficiency or autonomic involvement; helps confirm Lewy Body Dementia.

> *Breakthrough — blood test for Alzheimer's: In May 2025 the FDA cleared the Lumipulse G pTau217/Aβ42 blood test (Fujirebio) — the first blood test cleared to help diagnose Alzheimer's disease. Available commercially through Labcorp and Quest starting August 2025, the test detects amyloid pathology with accuracy comparable to amyloid PET or CSF — but from a simple blood draw. This is the most significant change in dementia diagnosis in decades.*

Cerebrospinal Fluid (CSF) Biomarkers

CSF testing — obtained via lumbar puncture — has been the established 'second standard' for confirming Alzheimer's biology when imaging is inconclusive. The three core markers are amyloid-beta 42, total tau, and phosphorylated tau (p-tau181, p-tau217). The AT(N) framework uses these markers to classify dementia biology rather than relying on symptoms alone.

Genetic Testing

Genetic testing is not routine but is recommended in specific situations:

- Early-onset dementia (before age 60)
- Strong family history suggesting autosomal dominant inheritance
- Before considering disease-modifying therapy (APOE testing — homozygous ε4 carriers face higher risk of brain edema and bleeding with Leqembi or Kisunla)
- Suspected FTD — testing for MAPT, GRN, C9orf72
- Family planning for those with known familial mutations

4. CURRENT MAINTENANCE MEDICATIONS

As of 2026, the medication landscape for dementia is divided into two very different categories:

- **Symptomatic medications** — available for decades, modestly improve cognition and behavior but do not slow underlying disease.
- **Disease-modifying therapies (DMTs)** — a new class of anti-amyloid antibodies approved in 2023–2024 that, for the first time, slow Alzheimer's progression by removing amyloid plaques. These are the most important development in dementia therapy in more than 20 years.

> *Important distinction: Disease-modifying therapy is currently available only for early Alzheimer's disease — not for Lewy Body, Vascular, or Frontotemporal Dementia. For those forms, treatment in 2026 remains symptomatic only. Trials for disease-modifying therapy in non-Alzheimer's dementias are underway (see Section 5).*

Class 1: Anti-Amyloid Antibodies (Disease-Modifying — Alzheimer's Only)

Anti-amyloid monoclonal antibodies bind to and clear beta-amyloid plaques from the brain. Multiple Phase 3 trials have shown they slow cognitive decline by approximately 27–35% over 18 months in early Alzheimer's. They are not cures, but they are the first therapies to alter the disease's biological course.

All carry a risk of amyloid-related imaging abnormalities (ARIA) — brain swelling or microbleeds visible on MRI. APOE ε4 carriers face higher risk, especially homozygotes (two copies). Treatment requires regular MRI monitoring.

Brand Name	Generic Name	FDA Approval	What It Does
Aduhelm	Aducanumab	2021 (withdrawn Jan 2024)	First anti-amyloid antibody approved. Withdrawn by Biogen in January 2024 amid controversy over efficacy and slow uptake.
Leqembi (IV)	Lecanemab	Jul 2023 (full approval)	Bi-weekly IV infusion. Slowed cognitive decline 27% over 18 months in Clarity AD Phase 3. The first DMT to receive traditional FDA approval.
Leqembi IQLIK	Lecanemab subcutaneous	Aug 2025	Once-weekly home subcutaneous injection. Same drug as IV Leqembi; eliminates infusion-

Brand Name	Generic Name	FDA Approval	What It Does
			center visits. Major convenience improvement.
Kisunla	Donanemab	Jul 2024	Monthly IV infusion. Slowed decline 22–35% in TRAILBLAZER-ALZ 2 Phase 3. Limited-duration treatment — patients may stop after amyloid is cleared.

Eligibility for anti-amyloid therapy requires (1) confirmed amyloid pathology via PET, CSF, or blood test; (2) early symptomatic Alzheimer's (MCI or mild dementia); (3) ability to undergo regular MRI monitoring. Both Leqembi and Kisunla are covered by Medicare Part B for eligible patients.

Class 2: Cholinesterase Inhibitors (Symptomatic)

Cholinesterase inhibitors (ChEIs) block the enzyme that breaks down acetylcholine — a neurotransmitter critical to memory and attention. They produce modest, temporary improvement in cognition for about 6–12 months in many patients and may slow decline for 1–3 years. They are first-line therapy for mild-to-moderate Alzheimer's and are also used in Lewy Body Dementia, Parkinson's Disease Dementia, and (off-label) Vascular Dementia.

Brand Name	Generic Name	Approval	Notes
Aricept	Donepezil	1996	Once-daily oral tablet (5–23 mg). Most widely used ChEI. Approved for mild, moderate, and severe Alzheimer's.
Exelon	Rivastigmine	2000 (oral) / 2007 (patch)	Available as oral capsule and 24-hour skin patch. The only FDA-approved drug specifically for Parkinson's Disease Dementia. Patch reduces GI side effects.
Razadyne	Galantamine	2001	Twice-daily oral or once-daily extended-release.

Brand Name	Generic Name	Approval	Notes
			Approved for mild-to-moderate Alzheimer's.

Common side effects include nausea, diarrhea, loss of appetite, vivid dreams, muscle cramps, and slowed heart rate. The patch form of rivastigmine substantially reduces GI side effects and is preferred for patients with swallowing problems.

Class 3: NMDA Receptor Antagonist (Symptomatic)

Memantine blocks NMDA glutamate receptors, which become overactive in moderate-to-severe Alzheimer's and contribute to neuron damage. It is typically added to a cholinesterase inhibitor as the disease progresses.

Brand Name	Generic Name	Approval	Notes
Namenda	Memantine	2003	Twice-daily oral or once-daily extended-release. Approved for moderate-to-severe Alzheimer's. Often added to donepezil.
Namzaric	Memantine + Donepezil	2014	Fixed-dose combination capsule of memantine ER + donepezil. Once daily; simplifies medication regimen.

Class 4: Antipsychotic for Dementia-Related Agitation

Agitation in Alzheimer's — restlessness, aggression, pacing, verbal outbursts — affects nearly half of all patients and is the most common reason families seek residential placement. Until 2023, no medication was FDA-approved for this indication, and clinicians relied on off-label antipsychotics carrying boxed warnings for increased mortality in dementia patients.

Brand Name	Generic Name	Approval	Notes
Rexulti	Brexpiprazole	May 2023	First and only FDA-approved medication for agitation associated with Alzheimer's dementia. Daily oral. Still carries

Brand Name	Generic Name	Approval	Notes
			class warning regarding increased mortality risk in elderly dementia patients.

Lewy Body Dementia — Approved and Off-Label Treatments

No drug has been FDA-approved specifically for Lewy Body Dementia. Treatment is built around cholinesterase inhibitors (rivastigmine is the best-studied) plus careful management of motor, sleep, and psychiatric symptoms.

- **Rivastigmine (Exelon):** Strongest evidence; FDA-approved for Parkinson's Disease Dementia, which shares pathology with LBD.
- **Donepezil:** Also commonly used; some patients tolerate better than rivastigmine.
- **Pimavanserin (Nuplazid):** Approved for Parkinson's disease psychosis; used off-label for hallucinations in LBD. Does not block dopamine and is safer for LBD patients than traditional antipsychotics.
- **Melatonin and clonazepam:** For REM sleep behavior disorder.
- **Levodopa:** Used cautiously for motor symptoms; can worsen hallucinations.

> *CRITICAL — Antipsychotic warning in Lewy Body Dementia: Patients with LBD can have severe, sometimes fatal sensitivity reactions to first-generation antipsychotics (haloperidol) and to some second-generation drugs (olanzapine, risperidone). Family members must inform every emergency room and hospital about the LBD diagnosis before any antipsychotic is given.*

Vascular Dementia — Treatment Approach

There are no FDA-approved drugs specifically for Vascular Dementia. Treatment focuses on (1) controlling vascular risk factors to prevent further brain injury, and (2) using Alzheimer's medications off-label when there is benefit.

- Aggressive blood pressure control (target typically <130/80)
- Statins for cholesterol
- Antiplatelet therapy (aspirin) or anticoagulation when indicated
- Diabetes management
- Smoking cessation, weight management, exercise
- Cholinesterase inhibitors and memantine — used off-label with modest benefit

Frontotemporal Dementia — Treatment Approach

No FDA-approved medication exists for FTD. Cholinesterase inhibitors can paradoxically worsen behavior in FTD and are generally avoided. Treatment is symptomatic:

- SSRIs (sertraline, citalopram) — for disinhibition, compulsions, food cravings
- Atypical antipsychotics (cautiously) — for severe agitation or aggression
- Speech and language therapy — particularly valuable in primary progressive aphasia
- Caregiver education and behavior management — often more effective than medication

Other Dementias — Specific Treatments

- **Korsakoff Syndrome:** High-dose thiamine (vitamin B1), abstinence from alcohol. Damage may be partially reversible if caught early.
- **Normal Pressure Hydrocephalus:** Ventriculoperitoneal shunt — surgical placement drains excess CSF. The only dementia with a potentially reversible cause.
- **Creutzfeldt-Jakob Disease:** No effective treatment. Supportive care only.
- **Huntington's Disease:** Tetrabenazine and deutetrabenazine for chorea (movements). Antidepressants and antipsychotics for psychiatric symptoms. No disease-modifying therapy approved.

5. PROMISING CLINICAL TRIALS — 2026 UPDATE

The mid-2020s represent the most active period of dementia research in history. Following the breakthrough approvals of Leqembi and Kisunla, dozens of new therapies are now in late-stage trials. Researchers are pursuing four core strategies: (1) clearing amyloid more efficiently, (2) targeting tau, (3) reducing brain inflammation, and (4) regenerating or protecting neurons. The most important news of 2025–2026 includes both major advances and significant disappointments — both essential to understand.

> *The hard truth of 2025: Two of the most-watched late-stage trials failed in 2025. Semaglutide (a GLP-1 drug widely used for diabetes and weight loss) failed its Phase 3 EVOKE/EVOKE+ trials for Alzheimer's in November 2025. Latozinemab — a progranulin-boosting therapy for genetic FTD — failed its INFRONT-3 Phase 3 trial in October 2025. Both were major disappointments. The field is responding by refining targets and combining approaches.*

Category A: Next-Generation Anti-Amyloid Therapies

With three anti-amyloid antibodies now approved or recently withdrawn, the focus has shifted to faster, safer, and more convenient versions.

Remternetug (Eli Lilly) — TRAILRUNNER-ALZ Trials

- Type: Next-generation anti-amyloid antibody, designed for more rapid amyloid clearance than Kisunla
- Trial: TRAILRUNNER-ALZ 1 (symptomatic AD) and TRAILRUNNER-ALZ 3 (preclinical AD — treating patients before symptoms appear)
- Status: Phase 3; topline data expected 2026–2027
- Why it matters: If effective in preclinical AD, this would establish prevention as the standard of care for at-risk individuals before any memory loss begins

Trontinemab (Roche / Genentech) — TRONTIER Trials

- Type: 'Brain shuttle' anti-amyloid antibody engineered to cross the blood-brain barrier 4–8x more efficiently
- Phase 1 / 2 results: 91% amyloid clearance at 28 weeks with ARIA-E rate of only ~1% (vs. 12–24% for current approved drugs)
- Trial: TRONTIER 1 and TRONTIER 2 Phase 3 trials launched fall 2025
- Why it matters: Potential to be dramatically safer than current anti-amyloid antibodies — the lower ARIA rate could expand eligibility, particularly for APOE ε4 homozygotes

Category B: Anti-Tau Therapies

Once amyloid is removed, tau pathology continues to drive neuron death. Anti-tau drugs aim to clear or silence the second major Alzheimer's protein.

E2814 / Etalanetug (Eisai)

- Type: Anti-tau monoclonal antibody targeting extracellular tau
- Status: FDA Fast Track designation September 2025; Phase 2 ongoing
- Why it matters: Eisai (maker of Leqembi) is positioning a tau therapy to combine with amyloid clearance — a two-drug approach modeled on cancer therapy

Diranersen / BIIB080 (Biogen / Ionis) — CELIA Trial

- Type: Antisense oligonucleotide (ASO) that reduces tau protein production in the brain — administered by lumbar puncture every 3 months
- Phase 2 result (CELIA, May 2026): Missed primary endpoint, but post-hoc analyses showed signals of benefit in specific subgroups. Biogen has stated it will advance to Phase 3 with refined design
- Why it matters: First ASO-based therapy to reach Phase 3 in Alzheimer's; could establish a new drug class for neurodegeneration

Bepranemab (UCB / Roche) and Posdinemab (Janssen)

- Both are anti-tau antibodies in Phase 2 testing
- Both target different segments of the tau protein, providing complementary approaches

Category C: Neuroinflammation and Repurposed Drugs

Buntanetap (Annovis Bio)

- Type: Oral once-daily drug; inhibits production of multiple neurotoxic proteins (amyloid, tau, alpha-synuclein, TDP-43) simultaneously
- Trial: Phase 3 in Alzheimer's; 65% enrolled as of March 2026
- Why it matters: Unique mechanism targeting multiple dementia pathologies at once — could theoretically benefit Alzheimer's, Lewy Body, and Frontotemporal Dementia

Semaglutide (Novo Nordisk) — EVOKE/EVOKE+ Trials

- Type: GLP-1 receptor agonist (same drug class as Ozempic/Wegovy)
- Status: Phase 3 EVOKE and EVOKE+ trials FAILED to meet primary endpoint, announced November 2025
- Why it matters: Despite the failure, GLP-1 drugs remain of interest for vascular and metabolic contributions to dementia; smaller trials continue with other GLP-1 agents

LM11A-31 / Bumitanide and Other Repurposed Candidates

- Multiple older drugs are being tested as potential disease-modifiers
- Advantage: Established safety profiles and lower development costs if effective

Category D: Gene Therapy

LX1001 (Lexeo Therapeutics) — APOE2 Gene Therapy

- Type: AAV-delivered gene therapy introducing protective APOE ε2 copies into the brains of APOE ε4 homozygotes (the highest-risk genetic group)
- Status: Phase 1/2; safety established; cognitive readouts expected 2026–2027
- Why it matters: If effective, this could potentially convert the highest-risk genetic profile into a protective one with a single treatment — a model for genetic dementia prevention

AVB-101 (AviadoBio) — Gene Therapy for GRN-Related FTD

- Type: One-time gene therapy delivering working copies of the GRN (progranulin) gene to the brain
- Trial: Phase 1/2 ongoing in patients with FTD caused by GRN mutations
- Why it matters: For genetic FTD, a single brain-delivered gene therapy could replace decades of decline with a one-time intervention

Category E: Lewy Body Dementia Trials

Neflamapimod (CervoMed)

- Type: Oral selective p38 alpha kinase inhibitor — reduces inflammation in cholinergic neurons
- Phase 2b result: Promising signals on cognition and motor function in mild-to-moderate Lewy Body Dementia
- Status: Phase 3 design pending FDA discussion
- Why it matters: Would be the FIRST drug specifically approved for Lewy Body Dementia

Category F: Frontotemporal Dementia — Aftermath of the 2025 Setback

In October 2025, Alector announced that latozinemab (AL001) failed its Phase 3 INFRONT-3 trial in GRN-mutation FTD. The drug had been one of the most-watched experimental therapies in dementia. Despite this setback, several other FTD programs continue.

- AL101 (Alector) — anti-amyloid mechanism in early trials
- AVB-101 gene therapy (above) — different mechanism than latozinemab
- Multiple anti-tau and anti-TDP-43 candidates in earlier development

Category G: Vascular Dementia Trials

Pure Vascular Dementia trials are limited, partly because of difficulty in patient selection. The most effective interventions remain aggressive treatment of cardiovascular risk factors. Trials of GLP-1 receptor agonists, SGLT-2 inhibitors, and PCSK9 inhibitors are evaluating prevention of cognitive decline in patients with diabetes and cardiovascular disease.

Trial Summary Table

Drug / Therapy	Target	Phase	Status	Expected Data
Remternetug	Amyloid (next-gen)	Phase 3	TRAILRUNNER-ALZ 1 & 3 enrolling	2026–2027
Trontinemab	Amyloid (brain shuttle)	Phase 3	TRONTIER 1 & 2 launched fall 2025; 91% clearance / ~1% ARIA in Phase 2	2027
E2814 / Etalanetug	Tau (extracellular)	Phase 2	FDA Fast Track Sept 2025	2026–2027
Diranersen / BIIB080	Tau (ASO)	Phase 2 → 3	CELIA missed primary May 2026; Phase 3 planned	2027–2028
Bepranemab	Tau	Phase 2	Ongoing	2026
Buntanetap	Multiple proteins	Phase 3	65% enrolled March 2026	2026–2027
Semaglutide	GLP-1 / metabolic	Phase 3	FAILED Nov 2025 (EVOKE/EVOKE+)	Completed
LX1001	APOE gene therapy	Phase 1/2	Safety established	2026–2027
AVB-101	Gene therapy (FTD-GRN)	Phase 1/2	Ongoing	2026–2027
Neflamapimod	p38α kinase (LBD)	Phase 2b → 3	Phase 3 design pending FDA	2027
Latozinemab (AL001)	Progranulin (FTD-GRN)	Phase 3	FAILED Oct 2025 (INFRONT-3)	Completed

> *How to evaluate clinical trial news: Promising Phase 2 results do not guarantee Phase 3 success — both latozinemab and semaglutide had encouraging earlier-phase data before failing late-stage trials. The most clinically meaningful results come from large, double-blind Phase 3 trials measuring outcomes that matter to families: function, behavior, time to nursing home placement, and total*

> *survival.*

6. THE CAREGIVER BURDEN

Organic Brain Syndrome is fundamentally a family disease. As cognition declines, family members — most often spouses and adult children, predominantly women — take on enormous caregiving responsibilities. The physical and emotional toll on dementia caregivers is more severe than for any other chronic illness.

13 million Americans serving as unpaid dementia caregivers in 2025

19+ billion hours of unpaid dementia care delivered in the U.S. in 2025

60+ hours/week typical caregiving load in advanced stages — far exceeding a full-time job

66% of dementia caregivers have at least one chronic health condition

40% of dementia caregivers report symptoms of clinical depression

63% higher mortality risk for spousal dementia caregivers vs. non-caregivers

877,000 unpaid dementia caregivers in Florida alone (2025)

What Caregivers Need to Know

- Caregiver burnout is not a sign of failure — it is a predictable outcome of an impossible burden sustained too long without support
- Respite care — temporary relief for caregivers — is available through Medicaid waiver programs in most states and through some community and veteran benefit programs
- Adult day programs provide structured daytime care for dementia patients while caregivers continue to work or recover
- Home health aides dramatically reduce caregiver strain and delay nursing home placement
- Support groups for both patients and caregivers are available through the Alzheimer's Association (alz.org) and local hospital systems
- Telephone helpline staffed 24/7 by master's-level clinicians: 1-800-272-3900 (Alzheimer's Association)

> *The caregiver who refuses help is the caregiver most likely to collapse — and the patient whose caregiver collapses is the patient most likely to enter residential care suddenly, in crisis. Investing in respite, adult day programs, and paid home help is not extravagance; it is risk management.*

7. KEY RESOURCES

Organization	What They Offer	Website
Alzheimer's Association	24/7 helpline (1-800-272-3900); local chapters; care consultation; caregiver education; clinical trial finder	alz.org
Lewy Body Dementia Association	Disease-specific education; physician referrals; family support; LBD research	lbda.org
Association for Frontotemporal Degeneration	FTD-specific education; helpline; support groups; genetic counseling resources	theaftd.org
NIH National Institute on Aging	Government health agency; dementia research; family resources; Alzheimer's & related Dementias Education and Referral Center (ADEAR)	nia.nih.gov
NIH ClinicalTrials.gov	Database of all active U.S. clinical trials; searchable by condition and location	clinicaltrials.gov
National Academy of Elder Law Attorneys (NAELA)	Locate an elder law attorney for advance directives and legal planning	naela.org
AARP	Caregiver resources and Medicare guidance	aarp.org
Eldercare Locator	Federal service connecting older adults and families to local services (1-800-677-1116)	eldercare.acl.gov
Family Caregiver Alliance	National caregiver support, education, and advocacy	caregiver.org

8. NEXT STEPS — GET THE HELP YOU NEED

> *Organic Brain Syndrome is the longest, most expensive, and most emotionally taxing of all chronic illnesses. The families who navigate it best are those who begin planning the moment a concern arises — before cognitive impairment closes the door on the patient's own decisions. You do not have to figure this out alone.*

If you or a loved one has cognitive symptoms, has been diagnosed with Mild Cognitive Impairment or early dementia, or is concerned about future risk, the following steps protect your family:

Step 1 — Get an Accurate Diagnosis

Cognitive symptoms have many causes. A board-certified neurologist or geriatric psychiatrist specializing in cognitive disorders will provide the most accurate diagnosis, identify the specific dementia type, rule out reversible causes, and connect you to current treatments and clinical trials. The Alzheimer's Association helpline (1-800-272-3900) can refer you to local specialists.

Step 2 — Execute Legal Documents Immediately

As soon as a cognitive concern exists, finalize:

- Durable Power of Attorney (financial) — allows a trusted person to manage finances
- Health Care Proxy / Durable POA for Healthcare — allows a trusted person to make medical decisions
- Living Will / Advance Directive — specifies wishes for end-of-life care
- Will and trusts as appropriate — updated to reflect current circumstances

These documents must be signed while the patient still has legal capacity. Once capacity is lost, the family must seek guardianship — a public, expensive, and stressful court process.

Step 3 — Consult an Elder Law Attorney

An elder law attorney can guide the family through advance directives, healthcare proxies, powers of attorney, wills, and trusts that reflect the patient's wishes — while the patient still has the legal capacity to sign them. The National Academy of Elder Law Attorneys (naela.org) maintains a state-by-state directory. Waiting even a few months can eliminate options that were available at the time of diagnosis.

Step 4 — Understand Available Community Resources

Many families do not realize how much community-based support already exists. The Alzheimer's Association helpline (1-800-272-3900) and the local Area Agency on Aging can connect families to adult day programs, respite services, support groups, care consultation, and veteran benefits. Building this map of resources early — before a crisis — means help is already in place when the family needs it.

Step 5 — Explore Clinical Trials

Clinical trials offer access to potential breakthrough therapies — often at no cost — while contributing to research that benefits all dementia patients. The Alzheimer's Association TrialMatch service (alz.org/trialmatch) and ClinicalTrials.gov are the best starting points. For Lewy Body Dementia, contact lbda.org; for FTD, contact theaftd.org.

Step 6 — Build Your Support Network

Connection with others facing the same journey is consistently cited by patients and families as one of the most valuable resources. Contact the Alzheimer's Association for local support groups, care center referrals, and the 24/7 helpline. Disease-specific organizations (Lewy Body Dementia Association, Association for Frontotemporal Degeneration) provide tailored support for those forms of dementia.

Step 7 — Care for the Caregiver

Schedule respite from the beginning — not after burnout. Use adult day programs, hire periodic help, attend caregiver support groups, maintain medical care for yourself, and accept help when offered. A caregiver who collapses cannot help anyone.

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