Progressively increasing life expectancy and declining fertility rates have led to a steady demographic shift towards the elderly population and consequently the prevalence of neurodegenerative diseases is on the rise. Alzheimer’s disease (AD) is the leading cause of dementia and about 0.5% of the global population or 35 million patients are currently afflicted worldwide. \(^1,2\) This number is expected to quadruple by the year 2050, with an attendant huge human and socioeconomic burden. \(^3\) Despite the disconcerting statistics, these are exciting times as we are at the cusp of better understanding of the disease with the promise of novel disease-modifying therapies (DMTs). To validate and standardize these biomarkers and select the most reliable, repeatable, easily available, cost-effective and complementary options is the challenge ahead.

**Introduction**

Progressively increasing life expectancy and declining fertility rates have led to a steady demographic shift towards the elderly population and consequently the prevalence of neurodegenerative diseases is on the rise. Alzheimer’s disease (AD) is the leading cause of dementia and about 0.5% of the global population or 35 million patients are currently afflicted worldwide. \(^1,2\) This number is expected to quadruple by the year 2050, with an attendant huge human and socioeconomic burden. \(^3\) Despite the disconcerting statistics, these are exciting times as we are at the cusp of better understanding of the disease with the promise of novel disease-modifying therapy (DMT). Simultaneously work is in progress on multi-target-directed ligands (MTDLs), hybrid drugs that act simultaneously on multiple targets, leading to greater therapeutic benefit and simplification of therapeutic regimens.

This article though not exhaustive in scope or detail, outlines the purported pathogenesis of the...
disease, the ongoing research in novel DMT drugs targeting different sites, and the role of diagnostics in detecting the disease in a preclinical state, monitoring disease progress and their complementary role in developing DMT.

**Pathogenesis of AD**

AD is a multifactorial disease and knowledge of the pathogenesis of AD is essential for understanding the role of diagnostics in its detection, monitoring and development of novel DMT. AD is associated with regional cerebral hypometabolism, extracellular Aβ plaques, intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau, neuroinflammation and oxidative stress, loss of synaptic connections, neural death and atrophy and resultant clinical manifestations of AD.

The progressive accumulation of Aβ and NFT is believed to begin more than 15 (Aβ) to 10 (NFT) years prior to onset of clinical disease.

Deposition of amyloid-β (Aβ) peptide in the brain is considered to represent the primary event in AD and the amyloid precursor protein (APP), a trans-membrane receptor, is central to the pathogenesis though its exact function is unknown. Aβ is generated by sequential proteolytic cleavage of APP by β-secretase or B-site APP cleaving enzyme (BACE)-1 from within and by γ-secretase from outside the membrane. When normally soluble Aβ peptides attain a definite level, they become insoluble, misfold and aggregate into Aβ plaques. These plaques are composed of insoluble peptides, generally 42 amino acids in length (Aβ42) and the oligomeric forms of Aβ42 are thought to have a greater neurotoxic potential than monomers or fibrils.

Cleavage of APP by the α-secretase followed by γ-secretase generates neuroprotective amyloid precursor protein (APPα). Apolipoprotein E (ApoE) ε4 allele of ApoE gene encodes the transporter of cholesterol in the brain and is the major genetic susceptibility factor for late-onset AD. AD is associated with higher membrane-associated free cholesterol and overall greater brain cholesterol load. Genetic mutations of APP (chromosome 21) or trisomy 21 cause early onset autosomal dominant AD. Mutations of presenilin-1, presenilin-2, clusterin (CLU), phosphatidylinositol-binding clathrin assembly protein (PICALM), complement component (3b/4b) receptor 1 (CR1) and triggering receptor expressed on myeloid cells 2 (TREM2) have also been found to be associated with the disease. While increased production of Aβ may cause early-onset AD, late onset AD may be caused by impaired Aβ clearance due to interactions with ApoEε4, reduced proteolysis, decreased transport across the blood-brain barrier, or inefficient cerebrospinal fluid (CSF) transport.

Tau binds and stabilizes microtubules and supports axonal transport. Tau interacts with Fyn in the postsynaptic compartment. Fyn phosphorylates the N-methyl-D-aspartate (NMDA) receptor subunit 2B (NR2B) and facilitates its interaction with postsynaptic density protein 95 (PSD95). The NR2B/PSD95 interaction is essential in Aβ-induced neurotoxicity. As increased neuronal membrane cholesterol is an important factor in AD and also causes overexpression of Fyn gene, this could be the link between cholesterol, Aβ and tau.

Casoli, et al. have proposed that mitochondrial DNA mutations are also important factors in AD. The two structural proteins NEDD9 (neural precursor cell expressed, developmentally down-regulated 9) and CAS9 (Cas scaffolding protein family member 4) and the kinase PTK2B (protein tyrosine kinase type 2 beta) apart from their roles in neoplasia, have been found to have a role in inflammation, hypoxia, vascular changes, microtubule stability and calcium signaling, and are relevant in AD.

Altered post-translational modification in the form of autophosphorylation of serine (Ser) and threonine (Thr), blocks the phosphorylation of tyrosine (Tyr) on insulin substrate receptor proteins (IRS) 1 and 2, impairs insulin signaling and leads to diabetes and AD-like complications. O-glycosylation of these Ser and Thr sites prevents phosphorylation and these sites may be targets for future drugs.

Metal dyshomeostasis has also been proposed as a contributing factor to the disease. Herpes simplex virus-1 (HSV) has been investigated as a potential cause of AD with a role of antiviral therapy in future. Deficiency of nutritional factors like docosahexaenoic acid (DHA) and vitamins have also been implicated in the causation of AD and are being investigated. People with higher educational attainment or socioeconomic status have been found to have a greater reserve against AD as do people who exercise regularly.

**Biomarkers**

The inaccessibility of the brain for histopathologic
confirmation and the long preclinical phase, make surrogate markers of the disease that provide a biological measure of the ongoing disease, irrespective of symptomatology, very important. This is especially so with the advances in DMT and hence these have been incorporated into the new diagnostic criteria for AD (albeit for research purposes only). These biomarkers can be genetic (ApoE genotype), biochemical (CSF or plasma) or imaging biomarkers. They have a role not only in early diagnosis and prognosis, but also in selection of subjects for shorter and smaller clinical trials with greater statistical power (selection of inclusion and exclusion criteria), in providing evidence of target engagement and disease-modifying effects of DMT (as surrogate end points) and in monitoring side-effects of DMT.

CSF biomarkers
Due to its direct contact with the brain extracellular space, CSF constituents closely reflect molecular events in the brain. Low CSF Aβ42 is a sensitive marker of cerebral Aβ deposition but it does not correlate well with duration or severity of disease. Low CSF Aβ is not very specific for AD as it is also seen in frontotemporal dementia (FTD), vascular dementia, Creutzfeldt–Jakob disease (CJD) and dementia with Lewy bodies (DLB). CSF tau (total-tau or t-tau and tau phosphorylated at threonine 181 or p-tau181) is increased in AD and its higher levels correlate with greater cognitive impairment. When Aβ42 and t-tau are considered together (Aβ42 to t-tau ratio), the sensitivity and specificity of diagnosing AD is more than 85%.33 Huded, et al. in a study from southern India also found that p-tau/t-tau and p-tau/Aβ ratio are good indicators of severity of dementia and may help differentiate between mild AD and moderate to severe AD.34 Different phosphorylated epitopes of tau may also be helpful in distinguishing AD and FTD (p-tau231) or AD and DLB (p-tau181).35,36

Levels of orexin (hypocretin), a neuropeptide that regulates arousal, wakefulness and appetite are altered in AD. Liguori, et al. have found that CSF orexin levels correlate with total tau protein levels, sleep impairment and cognitive decline in moderate to severe AD.37

Imaging biomarkers
The diagnostic value of imaging in AD is in identifying characteristic topographical, structural and functional alterations in the brain and in differentiating it from other causes of cognitive decline.

Volumetric magnetic resonance imaging (MRI)
AD is characterized by progressive atrophy of the medial temporal lobe (MTL) in a typical sequence: entorhinal complex, followed by hippocampus, amygdala, parahippocampus and posterior cingulate gyrus. Patients with atypical language and visual presentations have left temporal and occipital atrophy, respectively. Volumetric MRI (T1-weighted imaging) has been validated against pathological post-mortem markers such as Braak stages and is the most mature imaging biomarker of disease progression.38 Savva, et al. in their epidemiological-autopsy study of individuals with and without dementia found that though plaques, tangles and atrophy were all associated with dementia, atrophy was most strongly related to dementia.39 Progression of whole cerebral and hippocampal atrophy closely matches clinical worsening in AD.40 Visual evaluation of MTL atrophy vis-à-vis normal ageing has a sensitivity and specificity of around 80%-85%. Paradoxical hippocampal volume loss noted after anti-amyloid immunotherapy is likely due to amyloid removal and fluid redistribution rather than atrophy. Strict standardization is required for manual volumetry and automated software like FreeSurfer, learning embeddings for atlas propagation (LEAP), and QUARC analysis software. Haris, et al. in a small study have shown that T1rho MRI (a technique that can probe the protein content of various tissues) may be useful in the early diagnosis of AD.41

Vascular MRI
T2-weighted and fluid-attenuated inversion-recovery (FLAIR) images are used to identify amyloid-related imaging abnormalities (ARIAs, vasogenic edema and microhemorrhages) which are associated with Aβ-lowering drugs.42 Regulatory authorities require usage of vascular MRI for safety reasons in clinical trials using DMT. The occurrence of ARIAs is dependent on the dose of anti-Aβ drug and ApoEε4 genotype.43

Diffusion tensor imaging (DTI) MRI
DTI is based on the directionality of diffusion in the brain parenchyma and is used to assess white matter orientation and integrity using two parameters: fractional anisotropy (a marker of axonal integrity and myelination) and mean diffusivity (marker of cellular integrity). DTI can
supplement volumetric MRI by depicting characteristic disruptions in neuronal connections.44

**Functional MRI (fMRI)**
As the name suggests fMRI provides an insight into cerebral functioning. In this modality, statistical maps of cerebral activation are produced based on changes in regional microcirculation inferred from measuring changes in blood-oxygen-level dependent (BOLD) MR signal. The MRI signal changes because of changes in blood flow, volume and oxyhemoglobin/deoxyhemoglobin ratio induced by external stimuli, specific tasks or drugs. Decreased activity in the hippocampus/MTL and increased activity in the prefrontal cortex is seen during encoding of new information in patients with AD and prodromal AD.45,46

Increased activity may be sometimes seen in the MTL in the early stages of the disease and in individuals at genetic risk of AD, and this has been attributed to compensatory mechanisms during hippocampal failure.47 Apart from the MTL, memory function is also subserved by the “default mode network (DMN)” (precuneus, posterior cingulate, lateral parietal, lateral temporal and medial prefrontal regions).48 The DMN that normally exhibits beneficial deactivation in healthy subjects, shows increased activity in both preclinical and clinical AD patients.47,50

**Task-free resting-state fMRI (rs-fMRI)**
It is more easily applicable and places less technical demands than activation-task fMRI, especially in severely demented patients. Impaired DMN has been shown even on rs-fMRI and with a direct correlation to disease severity. rs-fMRI has been found to be a stronger classifier than activation-task fMRI in distinguishing risk groups in non-demented adults carrying familial AD genes.49

**Arterial spin labeling (ASL) MRI**
This is an fMRI technique for measuring tissue perfusion using magnetically labelled protons in blood as an endogenous contrast agent. ASL MRI in comparison with perfusion PET was found to be as informative about regional hypoperfusion in prodromal AD and symptomatic AD, with greater resolution and no radiation exposure.51,52 Although this modality is promising, standardization issues need to be addressed.18

**Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)**
PET involves detection of two oppositely directed annihilation photons generated by positron-emitting radiopharmaceuticals. FDG is a glucose analogue and enters cells by the same transport mechanism as glucose and is phosphorylated to FDG-6-phosphate (FDG-6-P). FDG-6-P does not enter into further enzymatic pathways and accumulates in the intracellular compartment proportional to the glycolytic rate of the cell. While FDG-PET is considered mainly a measure of synaptic activity, BOLD fMRI is indicative of integrated neuronal synaptic activity. The pattern of resting FDG hypometabolism in AD involving the limbic and association areas has been called an “endophenotype” of AD. These hypometabolic areas are highly vulnerable to Aβ deposition and the FDG pattern correlates with histopathology at autopsy.53 The extent and severity of FDG hypometabolism is predictive of conversion of prodromal AD to AD, and directly correlates with cognitive decline.54,55

**Amyloid PET**
Amyloid PET involves use of Aβ-selective radioligands that bind to fibrillar Aβ.18 F-FDDNP was the first PET tracer to be used in AD. Although there was higher retention of the tracer in the hippocampus, amygdala and entorhinal cortex of AD patients, it had a relatively high nonspecific binding and it also bound tau.56 The most commonly used tracer has been 11C-PiB (Pittsburgh Compound-B). However newer tracers that do not require a cyclotron like 18F-PiB and florbetaben, florbetapir and flutemetamol are being studied. In positive cases, Aβ deposits in a distribution that follows that of elevated aerobic glycolysis in the resting brain.57,58 Changes in amyloid PET can be seen as early as changes in CSF Aβ and so both may be used as screening tools, but as CSF Aβ reaches a final level early, amyloid PET is better at detecting cerebral amyloid load.53 The requirement of assessing disease progression is better served by structural MRI and FDG-PET vis-à-vis amyloid PET as amyloid deposition is an early event accumulating rapidly in the early stages and very slowly in the later stages.53,56 A direct correlation has been found between APOE4 and Aβ deposition (as measured with 11C-PiB) and on CSF Aβ1-42, but not on tau or p-tau181 levels, suggesting that Aβ initiates the disease.56 Aβ selective radioligands have also been used to provide
evidence of dose-dependent reduction of Aβ PET signal on treatment with bapineuzumab and gantenerumab; this was however not associated with clinical improvement. Another development has been development of tracers directed at NFT: 18F-T-807, 11C-PBB-3. Plasma protein biomarkers

MRI and PET are expensive investigations and CSF studies are invasive, consequently influencing repeatability. Plasma biomarkers have the potential to be easily accessible and cheap markers of disease status. Hye, et al. proposed a panel of plasma proteins as biomarkers that could be used to predict progression of mild cognitive impairment to AD [transferrin, CLU, cystatin C, A1 acid glycoprotein, complement C4, intercellular adhesion molecule (ICAM)-1, pigment epithelium-derived factor (PEDF), alpha-1 antitrypsin, regulated on activation normal T-cell expressed and secreted (RANTES), apolipoprotein C3] with an accuracy of 87% as well as proteins associated with greater atrophy [alpha-1 antitrypsin, neuron specific enolase, brain derived neurotrophic factor (BDNF), apolipoproteins (C3, A1, E)] in AD. However, these proteins need to be validated in more longitudinal studies and the issue of specificity addressed as many of these proteins may not be specific to AD. Nevertheless, the concept of a suitable panel of plasma protein and imaging biomarkers for early diagnosis and monitoring progress of AD appears promising.

These biomarkers are summarized in a tabular form in table 1.

Targets for DMT

The various targets of novel DMT can be broadly classified as a) interventions related to Aβ production, aggregation and clearance, b) immunotherapy against Aβ, and c) interventions related to tau hyperphosphorylation.

Interventions related to reduction of Aβ1-42 production, reduction of aggregation and increased clearance

BACE-1 is modified by bisecting N-acetylglucosamine (GlcNAc) and AD patients have increased bisecting GlcNAc on BACE-1. Kizuka, et al. have shown that deficiency of GlcNAc-transferase (GnT)-III, the biosynthetic enzyme for GlcNAc, reduces cleavage of Aβ by BACE-1 resulting in reduced Aβ plaques and improved cognitive function in animal models. Thus, GnT-III and notch-sparing 2nd generation γ-secretase inhibitors (e.g. begacestat, avagacestat, PF-3804014 and NICS-15) are promising candidates for DMT. Aβ levels can also be reduced by blocking BACE-1 and trials are on anti-β secretase antibodies. Thiazolidinedione anti diabetic drugs (rosiglitazone, pioglitazone) via peroxisome proliferator-activated receptor-γ (PPAR-γ) activation can suppress BACE-1 expression. However, a lack of conclusive beneficial effects and the attendant cardiac risks have led to termination of rosiglitazone trials for AD. The results with pioglitazone in a pilot clinical trial have also been conflicting. Another strategy can be upregulation of α-secretase activity, leading to increased neuroprotective APPα. Though some drugs are undergoing trials, no results are yet available.

As the neurotoxic potential of Aβ oligomers is greater than Aβ monomers or fibrils, antiaggregants like ELND005 (scyllo-inositol), tramiprosate (homotaurine) and PBT2 are also under investigation. Though ELND005 did not achieve the trial endpoints, it did produce changes in CSF Aβ. Similarly, tramiprosate (binds soluble Aβ) and PBT2 (impedes metal-induced oligomerization of Aβ) did not achieve trial endpoints.

Receptor for advanced glycation end-products (RAGE) mediates influx of Aβ and also mediates neuroinflammation and apoptosis, and low-density lipoprotein receptor-related protein 1 (LRP1) mediates efflux of Aβ from the brain. So their inhibitors and activators, respectively are targets of ongoing research. An oral RAGE-inhibitor (PF-0449700) has been tried but results were unsatisfactory. Another approach can be specific activation of proteases that degrade Aβ like neprilysin, insulin-degrading enzyme and plasmin.

Immunotherapy against Aβ

Two approaches are being pursued: active immunity (anti-Aβ vaccine) using compounds containing the N-terminal fragment of Aβ1-42 or N-terminus mimic peptides (ACC-001, CAD106, V950, AFFITOPE® AD02) and passive immunity using monoclonal anti-Aβ antibody (bapineuzumab, solanezumab). Though the clinical efficacy of bapineuzumab has not been consistent, it did demonstrate good tolerability with lowering of CSF p-tau and Aβ on PET. Solanezumab though not associated with ARIAs (amyloid-related imaging abnormalities), was also not found efficacious in mild to moderate AD.
<table>
<thead>
<tr>
<th>Name</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOEε4</td>
<td>Major genetic susceptibility factor for late-onset AD</td>
<td>Not diagnostic</td>
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<td>CSF Aβ1-42</td>
<td>Low Aβ1-42 is a sensitive marker of cerebral Aβ deposition</td>
<td>Genetic studies are expensive</td>
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<td>When Aβ1-42 and t-tau are considered together (Aβ1-42 to t-tau ratio), the sensitivity and specificity of diagnosing AD is more than 85%</td>
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<td>CSF orexin</td>
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<td>MRI</td>
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<td>MRI</td>
<td>Decreased activity in the hippocampus/MTL and increased activity in the prefrontal cortex is seen during encoding of new information in patients with AD and prodromal AD in Fmri</td>
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<td>MRI</td>
<td>rs-fMRI has been found to be a stronger classifier than activation-task fMRI in distinguishing risk groups in non-demented adults carrying familial AD genes</td>
<td>Not yet readily available</td>
</tr>
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<td>MRI</td>
<td>T2-weighted and FLAIR images are used to identify ARIAs which are associated with Aβ-lowering drugs</td>
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<td>FDG PET</td>
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<td>Amyloid PET</td>
<td>Changes in amyloid PET can be seen as early as changes in CSF Aβ and so both may be used as screening tools, but as CSF Aβ reaches a final level early, amyloid PET is better at detecting cerebral amyloid load</td>
<td>Issues of specificity need to addressed as many of these proteins may not be specific to AD</td>
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<tr>
<td>Plasma protein biomarkers</td>
<td>Potential to be easily accessible, cheap and repeatable</td>
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</table>

AD: Alzheimer’s disease; MRI: Magnetic resonance imaging; DTI: Diffusion tensor imaging; APOEε4: Apolipoprotein E ε4; CSF: Cerebrospinal fluid; FTD: Frontotemporal dementia; DLB: Dementia of Lewy bodies; MTL: Medial temporal lobe; fMRI: Functional MRI; rs-fMRI: Resting-state functional MRI; FLAIR: Fluid-attenuated inversion-recovery; ARIAs: Amyloid-related imaging abnormalities; ASL: Arterial spin-labeling; FDG: 18Fluoro-2-deoxy-D-glucose; PET: Positron emission tomography
However, these drugs may still have a role in AD prevention. Recent studies have shown that passive immunity achieved by using intravenous immunoglobulin (IVIG) has an acceptable safety profile with encouraging changes in body fluid biomarkers.\(^{73-75}\)

**Interventions targeted to tau hyperphosphorylation and aggregation**

Abnormally hyperphosphorylated and aggregated tau causes microtubule instability and axonal transport failure. Abnormal phosphorylation can be decreased by inhibiting tau kinases like glycogen synthase kinase (GSK)-3. GSK-3 inhibitors like valproic acid and lithium have not shown clinical efficacy or improvement in biomarkers. NP031112 (tideglusib), a non-ATP competitive GSK-3 inhibitor has been found to reduce p-tau and Aβ, prevent neuronal death and improve cognition in animals.\(^{76}\) Methylene blue (Rember\(^TM\)), an anti-tau aggregate and anti-oxidant has also been found to improve cognition in patients with mild to moderate AD.\(^{77}\)

**Bioengineering and gene therapy**

Research is also underway in bioengineering techniques using stem cells and gene therapy to induce neurogenesis, angiogenesis, axonal regeneration and neuronal replacement by producing a milieu of Aβ degrading enzymes and neural growth factors.\(^{78}\)

A number of studies from the Indian subcontinent have shown encouraging results from the use of medicinal herbs and antioxidants in AD in humans and animal models.\(^{79-81}\)

The various approaches for novel DMT are summarized in table 2.

<table>
<thead>
<tr>
<th>Class of drug/name</th>
<th>Mechanism of action</th>
<th>Special remarks</th>
</tr>
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<td>GnT-III and notch-sparring 2nd generation γ-secretase inhibitors (e.g. begacestat, avagacestat, PF-3804014 and NIC5-15)</td>
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<td>-</td>
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<td>Drugs upregulating α-secretase activity</td>
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<td>Inhibitor for RAGE</td>
<td>Specific activation of proteases that degrade Aβ</td>
<td>-</td>
</tr>
<tr>
<td>Activators of receptor for LRP-1</td>
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<td>-</td>
</tr>
<tr>
<td>Nepriylsin, insulin-degrading enzyme and plasmin</td>
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GlcNAc: N-acetylglucosamine; GnT: GlcNAc-transferase; APPα: Amyloid precursor protein; BACE-1: B-site APP cleaving enzyme; AD: Alzheimer’s disease; RAGE: Receptor for advanced glycation end-products; LRP: low-density lipoprotein receptor-related protein 1; GSK: Glycogen synthase kinase; PPAR-γ: Peroxisome proliferator-activated receptor-γ

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Conclusion

We have come far in our understanding of the pathogenesis of AD with rapid strides being made in diagnostic modalities to detect the disease at a preclinical stage when novel DMT may be instituted to halt disease progression and also to monitor the effects of these drugs. However, more multi-institutional and longitudinal data is required to validate and standardize these modalities and select the most reliable, repeatable, easily available, cost-effective and complementary options. Synergizing the multipronged efforts of multiple bodies and institutions as represented by AD Neuroimaging Network (ADNI) and Dominantly Inherited Alzheimer Network (DIAN) are the way forward.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.


References

Taming Alzheimer’s disease


