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REVIEW

Advances in Diagnostics and Treatments for Alzheimer's Disease

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Abstract

The rising prevalence of Alzheimer's disease (AD) with an aging population poses significant societal and healthcare challenges, leading to growing interest in strategies for early diagnosis and disease modification. This review synthesizes key developments in the diagnostic and therapeutic landscape of AD for general hospital clinicians. Diagnostic advances include improving the detection of hallmark biomarkers—amyloid beta (Aβ) and phosphorylated tau (p-tau)—via neuroimaging modalities, cerebrospinal fluid (CSF) analysis, and increasingly accessible plasma-based assays. Disease-modifying therapies which target amyloid, including Lecanemab and Donanemab, offer promising avenues but require close clinical monitoring due to associated risks such as amyloid-related imaging abnormalities (ARIA). While the amyloid and tau hypotheses continue to underpin much of the pathophysiological understanding of AD, current models also recognise the role of additional mechanisms such as chronic neuroinflammation and oxidative stress, broadening the scope for therapeutic targets. Collectively, these diagnostic and therapeutic advances represent a significant shift in AD early identification and management, with implications for the individual patient and the healthcare system.

Key words: Alzheimer's disease; biomarkers; cognition; dementia; mild cognitive impairment; molecular imaging; amyloid plaque

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Introduction

Dementia presents a huge dilemma for our health and social care system. Approximately 982,000 people are currently living in the UK with dementia. Due to our ageing population, this number is expected to rise to over 1.4 million and will cost £90 billion ($ 122.00 billion) by 2040 (Alzheimer's Society, 2024). Alzheimer's disease (AD) is by far the most common form of dementia, accounting for 60–70% of all dementia cases (Dementia Statistics Hub, 2023). This review article summarises recent advances in diagnosis and treatments for the general clinician.

Pathophysiology of Alzheimer's Disease

AD is a neurodegenerative disorder characterised by the accumulation of abnormal proteins in the brain, amyloid beta (Aβ) and tau. Extracellular amyloid plaques and intracellular neurofibrillary tangles (NfT), composed of phosphorylated tau (p-tau) filaments, cause damage to neurons and disrupt signalling between neurons.

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The damage and disruption lead to loss of synapses and neuronal death. This accumulates over time, resulting in brain atrophy.

While the simplicity of the amyloid and tau hypotheses was appealing and garnered traction in the 1990s, it is now increasingly recognised that there is a more complex interplay between proteins, oxidative stress, chronic neuroinflammation, insulin insensitivity, and neurovascular dysfunction behind the pathophysiology of Alzheimer's disease (AD). There is also accumulating evidence suggesting that intestinal microbiota plays a crucial role in AD pathogenesis and progression.

Advances in AD diagnosis focus largely on improving our ability to accurately detect the hallmark biomarkers of Aβ and p-tau through neuroimaging, cerebrospinal fluid (CSF) and plasma, while advances in AD treatment involve novel therapies to target and remove Aβ and p-tau, as well as targeting more recently appreciated pathways, such as chronic neuroinflammation.

Diagnosis: Advances in Diagnostic Criteria

Currently, AD is largely diagnosed by recognising a clinical phenotype built from piecing together patient and collateral history, cognitive testing and basic neuroimaging. This process relies on teams of specialist professionals, mostly in memory clinics, with appropriate training and expertise to differentiate between dementia types. This arguably lacks specificity and is not sensitive enough to identify disease in the early stages. The National Institute on Ageing-Alzheimer's Association (NIA-AA) have developed the Amyloid-Tau-Neurodegeneration (ATN) framework (Table 1) to incorporate objective, measurable biomarkers into the clinical diagnosis of AD. This approach sees AD as a continuum, from asymptomatic people with detectable changes in CSF and blood to those with visible atrophy on neuroimaging and observable clinical symptoms. Advantages of this framework include potential for earlier and faster diagnosis, better specificity, identifying those who are eligible for emerging treatments and more informed conversations regarding prognosis. However, the ATN framework is not universally accepted and has been criticised for its purely biological definition of AD. For example, in the 2024 revised criteria, they suggest a diagnosis of AD can be made in the presence of a Core 1 biomarker alone (Jack et al, 2024). This means people who are completely cognitively normal with no clinical symptoms can be labelled as having AD pathophysiology and could not go on to develop the disease.

Diagnosis: Neuroimaging

Neuroimaging is a necessary part of the workup for AD diagnosis. Volumetric measurement with Magnetic Resonance Imaging (MRI) of the hippocampus and posterior parietal lobes in particular can help identify the early stages of Alzheimer's spectrum disease (Jack et al, 2002). The severity of hippocampal atrophy can also help differentiate subtypes, as it is significantly greater in AD compared to other dementias such as Dementia with Lewy Bodies and Vascular Dementia (Barber et al, 1999). 18F-Flurodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) is able to differentiate AD from normal age-related changes and other dementias.

Table 1. ATN biomarker framework: 2024 revised criteria.

ATN biomarker class	Core level	Assessment method
A (Amyloid status)	Core 1 (early changing biomarkers): $A\beta_{42}$	Amyloid PET CSF biomarkers Plasma biomarkers
T (Tau status)	Core 1: p-tau217, p-tau181, p-tau231 Core 2 (later changing biomarkers): Other forms of p-tau (e.g., p-tau205) and non-phosphorylated tau fragments	Tau PET CSF biomarkers Plasma biomarkers
N (Neurodegeneration or neuronal injury)	Non-specific biomarkers involved in AD pathophysiology and non-AD co-pathology	FDG-PET Structural MRI CSF total tau (t-tau) Plasma biomarkers Infarction or white matter hyperintensity on MRI or CT

Each biomarker category can be marked as either positive or negative. An example of an individual's score might be recorded as "A+/T+/N-", indicating they are positive for amyloid and tau pathology on the above assessment methods, but negative for other biomarkers of neurodegeneration. Core levels are differentiated by the timing of abnormality onset and intended use, with Core 1 being early changing biomarkers and Core 2 being later-changing biomarkers.
Abbreviations: $A\beta_{42}$, amyloid beta 42; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; t-tau, total tau; PET, Positron Emission Tomography; FDG, Flurodeoxyglucose; MRI, Magnetic Resonance Imaging; CT, Computed Tomography.

Classically, glucose hypometabolism is observed in the temporoparietal lobes of people with AD on FDG-PET, particularly in the posterior cingulate and precuneus (Ishii, 2014). This ability to differentiate is important as patients with other types of dementia, such as fronto-temporal dementia (FTD), experience adverse side effects if treated with acetylcholinesterase inhibitors (Foster et al, 2007).

Diagnosis: Molecular Imaging for Diagnosis in Alzheimer's Disease

PET radiotracers to assess brain amyloid and tau deposition (Wolk et al, 2012) have also been developed. On amyloid PET imaging, the regional distribution of amyloid appears to closely replicate the distribution of amyloid plaques (Wong et al, 2010; Marcus et al, 2014). A positive amyloid PET scan can therefore provide evidence of the underlying neuropathology seen in AD, although there is increasing evidence of the role of amyloid deposition in other causes of cognitive decline (Rabinovici et al, 2025a). While this affects the imaging's positive predictive value, a negative amyloid-PET result is useful in excluding significant amyloid deposition and thus AD (Trembath et al, 2015). A positive scan can also help predict conversion from mild cognitive impairment (MCI) to AD (Suppiah et al, 2019).

Tau PET imaging has also been shown to be a strong indicator of diagnosis and predictor of subsequent cognitive decline in those with AD (Saint-Aubert et al, 2017). It has demonstrated prognostic value in patients with MCI (Ossenkoppele et al, 2021) to predict conversion to AD.

Diagnosis: CSF Biomarkers

CSF total tau (t-tau), p-tau, and Aβ_{42} are valuable as biomarkers of AD, and while their specificity reduces with age, their likelihood ratios are improved when CSF biomarkers are used in combination (Hansson et al, 2006). Currently, they are most clinically useful in supporting neurodegenerative etiology criteria for AD, and for predicting conversion from MCI to AD. A combination of CSF t-tau and Aβ_{42} yielded a sensitivity of 95% and a specificity of 83% for the detection of incipient AD in patients with MCI (Hansson et al, 2006).

Concordance between CSF biomarkers and amyloid PET imaging has been observed (for Aβ_{42}/Aβ_{40}, area under the curve (AUC): 0.90; 95% confidence interval (CI): 0.83–0.97; $p < 0.0001$), which confirmed that CSF biomarker analysis is a suitable alternative to PET imaging (Nisenbaum et al, 2023). In 2021, the International Working Group recommended CSF investigation be prioritised above amyloid and tau PET (Dubois et al, 2021). This is because CSF provides simultaneous information on Aβ and tau pathology, and is less expensive.

There have been necessary advancements in immunoassays used to detect biomarkers. The Lumipulse G and Elecsys platforms are approved in the US and Europe. They provide a fully automated immunoassay for CSF biomarker analysis, allowing for improved standardisation between centres (Laccarino et al, 2023). There is also ongoing work into expanding the number of proteins which can be examined in CSF and used as potential biomarkers for AD. A protein panel targeting 48 CSF proteins used alongside existing CSF biomarkers helped improve diagnostic performance and predict future dementia severity (Haque et al, 2023).

Diagnosis: Plasma Biomarkers

Understandably, the prospect of the CSF biomarkers is less appealing to patients as the fluid has to be obtained via lumbar puncture (LP). One patient survey found 91% of respondents were willing to have a scan, but only 43% willing to have an LP (Alzheimer's Research, 2019). For this reason, advancements in plasma biomarker testing have been driven by the need for a less expensive and less invasive method to obtain biomarkers.

Similar to CSF samples, there are now fully automated immunoassays for Aβ detection, which correlate highly with "gold standard" immunoprecipitation mass spectrometry (IP-MS) (Yamashita et al, 2021).

Encouraging results are also being found in the detection of tau isomers, with p-tau217 emerging as a frontrunner for accurate detection in plasma. Plasma p-tau217 is demonstrably as good or superior to CSF biomarkers at correlating with amyloid PET positivity (Barthélemy et al, 2024). The 'Blood Biomarker Challenge' has been launched in the UK and is funding two studies, the REAl World Dementia

OUTcomes (READ-OUT) trial and the Alzheimer's disease Diagnosis And Plasma p-Tau217 (ADAPT) trial. Their broad aim is to provide data supporting the use of plasma biomarkers in the National Health Service (NHS) for improving the speed and accuracy of diagnosis in the UK.

Advances in Treatment

Current medications for AD are classed as symptomatic treatments. They aim to slow disease progression and alleviate cognitive and behavioural symptoms of dementia, but do not cure, prevent or alter the underlying pathology. First line, for mild AD, are acetylcholinesterase inhibitors, which increase levels of available acetylcholine in the synaptic cleft. Memantine was approved for moderate to severe AD. It is an N-methyl-D-aspartate (NMDA) receptor antagonist which aims to reduce the overstimulation of the NMDA receptor by glutamate.

The hunt has been ongoing for decades for disease-modifying therapies (DMT); drugs which can prevent or reverse the disease. Following several amyloid-targeted treatments with limited success, the role of biological agents, namely monoclonal antibodies, was explored as a potential for disease modification in AD. While several monoclonal antibodies were developed, a series of failures in phase III trials cast doubt about their use in disease modification and whether the amyloid cascade was a sensible target after all.

Advances in Treatment: Monoclonal Antibody Therapies

Aducanumab

Despite their initial lack of success, Aducanumab, a monoclonal antibody targeting both the insoluble and soluble forms of Aβ, showed early promise. When using the Clinical Dementia Rating Scale—Sum of Boxes (CDR-SB), an 18-point, semi-structured interview of patients and carers which quantifies the severity of the symptoms of dementia, high-dose Aducanumab administration was associated with a 22% reduction in scores (a difference of 0.39 points when compared to placebo, $p = 0.012$) at 78 weeks (Yuksel et al, 2022). However, another large phase III trial (Budd Haeberlein et al, 2022) was discontinued as the effect on plaque reduction was felt unlikely to translate into clinical endpoints. Despite conflicting evidence regarding its clinical benefit, Aducanumab was approved by the U.S. Food and Drug Administration (FDA) in 2021.

Donanemab

Donanemab, another humanised monoclonal antibody which targets pGlu3-Aβ, offers further promising prospects for the management of AD.

In a randomised phase II trial, Donanemab use was associated with a modest reduction in cognitive decline as assessed by the Integrated AD Rating Scale (iADRS), but when assessed with the CDR-SB score as a secondary outcome, the study failed to show a significant difference between the two trial groups. Additionally, Donanemab was associated with slowing of clinical progression, and it

was estimated that those who received Donanemab saved 4.4–7.5 months over 18 months (Mintun et al, 2021).

In TRAILBLAZER-ALZ 2 (A Study of Donanemab (LY3002813) in Participants With Early Alzheimer's Disease, NCT04437511), a phase III trial, Donanemab treatment resulted in clinically meaningful benefit on both the iADRS and CDR-SB scales for both the low/medium tau and combined populations. In those treated with Donanemab, amyloid clearance was seen in 76.4% at 76 weeks (compared with 0.3% with placebo) (Sims et al, 2023).

Lecanemab

Lecanemab, a humanized monoclonal antibody of immunoglobulin G1 (IgG1), has been shown to bind with high affinity to soluble Aβ protofibrils primarily. In CLARITY AD (A Study to Confirm Safety and Efficacy of Lecanemab in Participants With Early Alzheimer's Disease, NCT03887455), a phase III trial, Lecanemab resulted in a significant reduction in markers of amyloid in early AD, evidenced by PET imaging and CSF testing (van Dyck et al, 2023).

Furthermore, Lecanemab use was associated with demonstrable improvement on measures of function when compared to placebo at 18 months (van Dyck et al, 2023). The CDR-SB was also measured as the primary efficacy endpoint, and Lecanemab use was associated with an adjusted least-squares mean change from baseline of 1.21 (vs. 1.66 with placebo). This difference of 0.45 was significant, but it is unclear what the clinical benefit of this change will be. We await the results of ongoing open-label phase studies for more clarity.

Important Considerations of Currently Available Monoclonal Antibodies

The minimally clinically important difference (MCID) describes the smallest change in a treatment outcome that patients perceive as beneficial. While MCID values increase with disease severity, a 1–2 point increase in CDR-SB has been reported to show clinician-indicated meaningful change (Andrews et al, 2019). So, while these monoclonal antibodies were the first potential amyloid-modifying treatments that showed statistically significant results in clinical outcome measures, it remains unclear if their results will confer clinical benefit to both patients and caregivers. In terms of route of administration, while current anti-dementia treatments are the more convenient oral or transdermal preparations, Lecanemab and Donanemab are given as IV infusions. Lecabemab is given 2-weekly until progression to moderate AD has occurred. Donanemab is given 4-weekly via IV infusion for 18 months or until amyloid PET is negative.

In addition, anti-Aβ immunotherapies have been associated with serious adverse events called amyloid-related imaging abnormalities (ARIA). ARIA is categorised by microhaemorrhages and superficial siderosis (amyloid-related imaging abnormalities-haemosiderin deposition [ARIA-H]) or by oedema and effusions (amyloid-related imaging abnormalities-oedema and effusion [ARIA-E]). In the CLARITY AD study, Lecanemab was associated with ARIA-H in 17.3% (vs. 9% with placebo), and ARIA-E in 12.6% (vs. 1.7% with placebo) (van Dyck et al, 2023). The majority were asymptomatic, but 0.8% of the participants had ARIA-E

listed as a serious adverse event. Donanemab's side effect profile includes headaches, infusion reactions and ARIA. ARIA-E was reported in 24% (vs. 1.9% with placebo), and ARIA-H was reported in 19.7% (vs. 7.4% with placebo). While these were noted to mostly be mild or asymptomatic, death occurred in 3 patients (0.4% with placebo) of those receiving treatment (vs. 1 in the placebo group) (Mintun et al, 2021). Their side effect profiles have led to extensive appropriate use recommendations (AUR) and tight inclusion and exclusion criteria, which have been summarised in Table 2. Importantly, those on anticoagulants or with a recent history of strokes/Transient Ischemic Attacks (TIAs) should not be treated (Rabinovici et al, 2025b).

In addition, in view of the risk of ARIA, it was recommended that all patients should have several safety MRI scans (Cummings et al, 2021). Patients who are apolipoprotein E ε4 (*APOE4*) gene carriers, especially *APOE4* homozygotes, are at higher risk for ARIA, and the AUR recommends *APOE* genotyping to better inform risk discussions with patients who are treatment candidates.

The significant risk profiles associated with the use of Lecanemab and Donanemab raise several ethical considerations, including the need to balance their potential for significant side effects with their potential for benefit, which will likely remain complex and uncertain, and to then ensure informed consent. There are also several practical considerations, including the potential need to restructure services to allow administration of biomarker-guided therapy requiring new diagnostic pathways, while also ensuring fair and equitable access for all NHS patients. Furthermore, there is the potential for additional stress on already stretched services associated with the need for regular infusions and the intensive monitoring requirements for serious adverse effects.

In the UK, the cost of providing the medication was felt to not be good value for the taxpayer when balanced with the relatively small patient benefit, and they were not approved by the National Institute for Health and Care Excellence (NICE) for NHS use (NICE, 2025). In England, approximately 70,000 adults would have been eligible for treatment with Donanemab, and the cost would have exceeded £1 billion (1 GBP = 1.34 USD) per year (NICE, 2024).

Outside of the UK, following approval by the European Medicines Agency (EMA) in 2024, the European Union (EU) Commission has granted EU authorisation for Lecanemab use, but has recommended the refusal of the marketing authorisation for Donanemab use. This is under ongoing re-examination (De Strooper et al, 2025). Both Lecanemab and Donanemab were approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) in 2024 for adults in the early stages of AD who have one or no copies of the apolipoprotein E ε4 (*APOE4*) gene. Lecanemab is also available in the USA, Japan, and China, and open-label extension trials are ongoing (van Dyck et al, 2023).

Table 2. Mechanism of action, global approval status, inclusion and exclusion criteria, monitoring requirements, adverse reaction rates and drug discontinuation mechanisms for both Donanemab and Lecanemab based on their respective appropriate use recommendations.

	Donanemab	Lecanemab
Mechanism of action	Humanised monoclonal antibody which targets pGlu3-Aβ.	Humanized monoclonal antibody has been shown to bind with high affinity to soluble Aβ protofibrils primarily.
Global approval status	Full FDA approval. Licensed for MHRA in the UK, not for *APOE4* homozygous. Marketing of Donanemab is not recommended by EMA.	Full FDA approval. Licensed for MHRA, not for *APOE4* homozygous. Approved by EMA.
Adverse reaction rates	ARIA-H in 19.7% (vs. 7.4% with placebo). ARIA-E in 24% (vs. 1.9% with placebo). Infusion-related reaction in 7.6% (vs. 0% with placebo).	ARIA-H in 17.3% (vs. 9% with placebo). ARIA-E in 12.6% (vs. 1.7% with placebo). Infusion-related reactions in 26.4% (vs. 7.4% with placebo).
Inclusion criteria	MCI or mild dementia due to AD. Confirmed AD biomarkers on Amyloid PET or CSF. Physician judgment is used for patients outside the 60–85 years age range.	MCI or mild dementia due to AD. Confirmed AD biomarkers on Amyloid PET or CSF. Physician judgment is used for patients outside the 50–90 years age range.
Exclusion criteria	On anticoagulants (including dabigatran, rivaroxaban, apixaban, and or heparin). Medical history including uncontrolled bleeding disorders, psychiatric disorders that could interfere with comprehension, history of immunologic disease or current systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies or their derivatives. Patients with stroke or transient ischemic attack within the past 12 months or any history of seizures.	On anticoagulants (including dabigatran, rivaroxaban, apixaban, and or heparin). Medical history including uncontrolled bleeding disorders, psychiatric disorders that could interfere with comprehension, history of immunologic disease or current systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies or their derivatives. Patients with stroke or transient ischemic attack within the past 12 months or any history of seizures.

Table 2. Continued.

	Donanemab	Lecanemab
Exclusion criteria on baseline MRI	More than 4 cerebral micro-haemorrhages. Any intracerebral haemorrhage greater than 1 cm or severe white matter disease. Any area of superficial siderosis. Territorial infarcts >1 cm. >2 lacunar infarcts. Presence of ARIA-oedema/effusion. Evidence of Cerebral amyloid angiopathy-related inflammation. Cerebral contusion. Encephalomalacia. Brain aneurysms or other vascular malformations. Brain tumours, except for small meningiomas or arachnoid cysts.	More than 4 cerebral micro-haemorrhages. Any intracerebral haemorrhage greater than 1 cm. Any area of superficial siderosis. Stroke involving a major vascular territory. >2 lacunar infarcts. Evidence of vasogenic oedema. Severe subcortical hyperintensities consistent with a Fazekas score of 3. Evidence of ABRA. Evidence of cerebral amyloid angiopathy-related inflammation.
MRI frequency	Screening MRI within 12 months of treatment initiation. Surveillance MRIs prior to the 2nd, 3rd, 4th and 7th infusions. Additional MRI prior to the 12th dose in higher-risk individuals.	Screening MRI within 12 months of treatment initiation. Surveillance MRIs after the 5th, 7th, and 14th infusions. Additional MRI prior to the 26th infusion in high-risk individuals.
Other monitoring requirements	*APOE* genotyping prior to treatment to inform an individual's risk of developing ARIA.	*APOE* genotyping prior to treatment to inform an individual's risk of developing ARIA.
Drug discontinuation mechanisms	Treatment is given for 18 months. Clinicians may also consider discontinuing treatment if amyloid clearance is demonstrated by amyloid PET, which is typically obtained 12–18 months after initiating treatment.	Treatment with Lecanemab has been recommended to be discontinued once the patient progresses to moderate AD.

Abbreviations: ABRA, amyloid beta-related angiitis; AD, Alzheimer's disease; *APOE*, apolipoprotein E; ARIA-H, amyloid-related imaging abnormalities-haemosiderin deposition; ARIA-E, amyloid-related imaging abnormalities-oedema and effusion; CSF, cerebrospinal fluid; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCI, mild cognitive impairment; MHRA, Medicines and Healthcare Products Regulatory Agency; PET, Positron Emission Tomography.

Advances in Treatment: Tau-Targeted Therapies

Evolution in our understanding of the pathophysiology of AD has also led to new drug targets which explore and address other pathological hallmarks of AD. Tau aggregation inhibitors.

Tau aggregation inhibitors prevent the accumulation of p-tau into toxic oligomers and NfTs. Methylene blue and its derivatives showed promise in pre-clinical studies in preventing the aggregation of tau (Congdon et al, 2012) and suggested that methyl blue could protect against tau-mediated neuronal damage. Building on the potential of Methylene blue, leuco-methylthioninium (LMTM) was developed as a more stable, better absorbed derivative and advanced to clinical trials. Despite promising pre-trial data, two phase III clinical trials testing LMTM as an adjunct and as monotherapy in participants with mild to moderate AD failed to show significant benefits in slowing cognitive decline (Gauthier et al, 2016; Wilcock et al, 2018). A phase II trial over 18 months in a non-randomised cohort of patients with mild Alzheimer's also found no significant improvement in clinical outcomes (Wischik et al, 2015), although a significant decline in the rate of brain atrophy at 9 months was reported.

Tau Kinase Inhibitors

An imbalance of kinases and phosphatases, which respectively add and remove phosphate groups to proteins, is seen in AD. Overactive kinases or underactive phosphatases are thought to be one cause of hyperphosphorylation of tau.

Glycogen Synthase Kinase-3β (GSK-3β)

Glycogen Synthase Kinase-3β (GSK-3β) is a kinase found to be overactive in AD. Interestingly, GSK-3β is also implicated in Aβ deposition. Tideglusib and Lithium both inhibit GSK-3β, and pre-clinical studies were promising in both. However, phase II trials of Tideglusib in mild to moderate AD did not demonstrate significant clinical benefits (Lovestone et al, 2015). Lithium has not been advanced to any clinical trials.

Mitogen-Activated Protein Kinase (MAPK)

Mitogen-Activated Protein Kinase (MAPK) is a family of kinases involved in many signalling pathways in the central nervous system (CNS). MAPKs are involved in the generation and deposition of Aβ plaques, tau protein phosphorylation, oxidative stress, and cholinergic neurotransmission, all of which are key players in the development and progression of AD. The p38α MAPK plays a particular role in tau phosphorylation, and inhibiting p38α MAPK reduces tau phosphorylation, decreases inflammatory markers and improves memory in mouse models (Maphis et al, 2016). In phase II clinical trials, 24 weeks of treatment with a p38α MAPK inhibitor (Neflamapimod) lowered CSF biomarkers of t-tau and p-tau, but there were no significant clinical improvements on cognitive tests (Prins et al, 2021).

Tau Immunotherapy

Tau immunotherapy aims to recruit the body's own immune system to bind and clear tau aggregates and NfTs. Immunotherapies can be deemed "passive" or "active". In passive immunotherapies, the body is given a ready-made antibody, or a monoclonal antibody (mAb), designed to target any kind of tau, including monomers, oligomers or fibrils. In active immunotherapy, the patient's own immune system is trained to recognise and attack tau via vaccination. This method is slower, but the results are more durable as the patient's immune system retains a memory of this response.

Passive Immunotherapy

Early first-generation anti-tau mAbs such as Semorinemab, Tilavonemab, Gosuranemab, and Zagotenemab were well tolerated, but there were no clinical benefits for patients with early AD. This was potentially because it is difficult for mAbs to pass the blood-brain barrier (BBB), but they also only targeted one end of the tau protein. Newer mAbs are focusing on targeting the middle region of the tau protein, as this may be crucial for aggregate formation (Guo et al, 2024) and seems to be more effective for the prevention of tau spread (Nobuhara et al, 2017). One such mid-region targeting mAb is Bepranemab (UCB0107). Preclinical trials found Bepranemab blocked tau seeding and neutralised pathological tau in mice (Guo et al, 2024).

TOGETHER, a phase 2a double-blind study (NCT04867616) was started in 2021. This study assesses Bepranemab use in patients with prodromal to mild AD. A total of 466 patients took part in the study, for a duration of 80 weeks, and aims to be completed by 2028 (Citron et al, 2024).

Similarly, another mid-region mAb (JNJ-63733657) has entered phase II clinical trials (NCT04619420) and is expected to complete by 2032. The primary purpose of this study is to evaluate the effect of JNJ-63733657 versus placebo on clinical decline measured by iADRS (Citron et al, 2024).

Active Immunotherapy—Tau Immunisation

There are two anti-tau vaccines currently in clinical trials. AADvac1 (Safety Study of AADvac1, a Tau Peptide-KLH-Conjugate Active Vaccine to Treat Alzheimer's Disease, NCT01850238) phase I trials showed the vaccine was safe, and hippocampal atrophy was slower in participants with high immunoglobulin G (IgG) antibody response (Novak et al, 2018). A larger study in 2021 replicated the strong and sustained immunological response but failed to show any clinical benefit on cognitive testing (Novak et al, 2021).

The ACI-35 vaccine reduced tauopathy in mice (Theunis et al, 2013) and is considered safe for the treatment of MCI and mild AD after phase Ib/IIa clinical trial (NCT04445831). The FDA has granted fast-track designation to ACI-35 and a phase IIb trial, RETAIN, launched in December 2023, aiming to study the vaccine in up to 500 patients over 4 years.

Advances in Treatment: Reducing Chronic Neuroinflammation

Neuroinflammation is the brain's defence against foreign pathogens and disease. It is a complex cascade of processes which primarily involve glial cells (microglia and astrocytes) and the release of pro-inflammatory chemical messages (e.g., tumour necrosis factor α [TNF-α], interleukins, interferons, and chemokines). Microglia are the brain's immune cells for clearing harmful substances, like Aβ. They also release messengers, called cytokines, which orchestrate the immune response by communicating with other immune cells. While this is helpful for clearing an acute infection, prolonged activation of microglia and prolonged release of cytokines start to contribute to neuronal damage. In AD, the presence of Aβ plaques and p-tau causes this prolonged activation of microglia and cytokines, causing more deposition of Aβ and p-tau, leading to a vicious cycle of disease progression. Addressing chronic neuroinflammation has therefore become an exciting area of potential drug therapies.

Improving Microglial Clearance

There are over 30 gene variants associated with an increased risk of developing late-onset AD. Many of these gene variants are highly expressed in microglia and can impair their ability to degrade Aβ plaques. Therefore, antibodies have been designed to target these genetic variants and improve microglial function. Specific gene targets for pharmaceutical research have been genetic variants in: Triggering Receptor Expressed on Myeloid Cells 2 (*TREM2*), ATP Binding Cassette Subfamily A Member 7 (*ABCA7*), Complement Receptor 1 (*CR1*) and Cluster of Differentiation 33 (*CD33*).

Triggering receptor expressed on myeloid cells 2 (TREM2) is expressed in the brain predominantly by microglia and is crucial for microglial function in the brain. AL002 is a humanized monoclonal IgG1 antibody (mAb) that activates the TREM2 receptor, and has been shown to reduce Aβ plaques, reduce neuronal loss and improve cognitive function in mice (Wang et al, 2020). In a phase 1 study of 64 healthy volunteers (INVOKE-1), AL002 infusion was associated with an increase in biomarkers of microglia recruitment, and was well tolerated with no serious adverse events recorded over 12 weeks (Long et al, 2024). A phase II trial, INVOKE-2 (NCT04592874), where IV infusion was given every 4 weeks, for up to 96 weeks, was completed in September 2024 (Alector, 2025).

In this study, AL002 failed to slow AD progression as measured with CDR-SB, with no significant effects on AD biomarkers or reduction of brain amyloid levels on PET imaging. In addition, MRI changes resembling amyloid-related imaging abnormalities (ARIA) and infusion-related reactions were observed.

Modulating the Microglia Phenotype

Microglia exist in different states, M1 (pro-inflammatory) and M2 (anti-inflammatory). By switching microglia from M1 to M2, researchers have hypothesised that chronic neuroinflammation can be dampened. Sargramostim stimulates bone

marrow to produce more microglia in the non-inflammatory M2 state. Preclinical results suggested it was effective in reducing Aβ and reversing cognitive decline in mice. A phase II study in mild to moderate AD showed Sargramostim was effective at reducing plasma Aβ, tau and neurodegeneration marker Ubiquitin C-terminal hydrolase L1 (UCHL1); however, cognitive benefits were modest at 45 days, and did not meet statistical significance at the 90-day follow-up (Potter et al, 2021). Another phase II study (NCT04902703) is currently being recruited for and aims to be completed by 2026.

Targeting the Inflammatory Mediators

Targeting the pro-inflammatory cytokines themselves is another way to reduce chronic neuroinflammation. Canakinumab is a monoclonal antibody designed to target and block a cytokine in the inflammatory cascade called interleukin-1β (IL-1β). It is currently included in a phase II platform study to evaluate the safety and tolerability of anti-inflammatory agents (NCT04795466) (Tondo et al, 2024).

Masitinib is a tyrosine kinase inhibitor which targets mast cells and microglia. A randomised, double-blind, placebo-controlled study with two parallel groups found significantly slowed cognitive decline compared to placebo on the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) at 24 weeks when Masitinib was taken alongside established AD treatments (Dubois et al, 2023).

Advances in Treatment: Glucose Metabolism and Insulin Insensitivity

Another theorised mechanism of the development and progression of AD involves the connection between oxidative stress and impaired glucose metabolism. It is thought, Aβ_{42} aggregates sit in cell membranes and are highly toxic, directly promoting oxidative stress, which changes the structure of proteins and lipids, rendering them ineffective (De et al, 2019). This process can impair the action of enzymes involved in glycolysis and can contribute to insulin resistance. When this occurs, there is less energy for the brain, and neurons struggle to meet their high energy demands.

Metformin

Metformin increases insulin sensitivity in people with type 2 diabetes mellitus (T2DM) and has been investigated for potential benefits in AD. Results have been mixed so far (Rosell-Díaz and Fernández-Real, 2024), with promising preclinical results often not translating to human studies. There is one active study (NC104098666) looking at Metformin and Alzheimer's dementia prevention, hoping to enrol 326 participants into a randomised control trial (RCT) of long-acting metformin vs. a matching placebo. Study completion is expected in 2027.

Glucagon-Like-Peptide 1 Receptor Agonists (GLP-1 RAs)

Activation of the Glucagon-Like-Peptide 1 (GLP-1) receptor stimulates insulin secretion, overcoming insulin resistance. Researchers from Denmark (Nørgaard et al, 2022) pooled data from three large RCTs, including a total of 15,820 partic-

ipants and found GLP-1 Receptor Agonists (RAs) were associated with reduced risk of dementia compared to placebo. They also looked retrospectively at data from a nationwide registry-based cohort (120,054 participants) and observed a reduced incidence of dementia in patients with T2DM treated by GLP-1 RAs. Evoke (NCT04777396) and Evoke+ (NCT04777409) are both large, multicentre phase III trials spanning 38 countries. Their primary outcome is to confirm Semaglutide (a GLP-1 RA) is more effective at improving cognition and function in patients with mild AD, compared to placebo. They are expected to complete in 2026.

Insulin

Unlike Metformin and GLP-1 RAs, insulin has the benefit of being able to cross the blood-brain barrier (BBB). However, when administered peripherally, it also increases the risk of causing hypoglycaemia. Intranasal insulin is under investigation as a possible new treatment as it retains the benefit of being able to cross the BBB, without the risk of hypoglycaemia. An early RCT study found intranasal insulin improved cognition in early AD and reduced levels of Aβ_{42} (Craft et al, 2012); however, no long-term cognitive or functional benefits were found after 12 months (Craft et al, 2020). There is an active phase II trial (NCT06072963) currently recruiting to look at the effect of combining intranasal insulin with Semaglutide, aiming to complete by 2028.

Other Agents

NE3107 is an insulin-sensitiser which has also demonstrated anti-inflammatory benefits. It can pass through the BBB and has been demonstrated to be safe in both animal and human studies (Reading et al, 2021).

Conclusion

The increasing prevalence of AD in our aging population has widespread societal implications, which have led to increasing interest in early and accurate diagnoses and in disease-modifying therapy. Advances in AD diagnosis remain focused on improving our ability to accurately detect the hallmark biomarkers of AD, including Aβ and p-tau, through neuroimaging, CSF and plasma. While the amyloid and tau hypotheses remain key theories in understanding the underlying pathology in AD, it is widely accepted that there are other complex processes involved, including chronic neuroinflammation and damage from oxidative stress, giving researchers more molecular targets for therapies. This opens new avenues for disease-modifying treatments and remains a significant area of interest for future research.

Key Points

- In addition to structural imaging, Amyloid and tau PET imaging is recognised to have a diagnostic value in AD, and in patients with MCI to predict conversion to AD.
- CSF biomarkers show high concordance with FDG-PET imaging, but require LP to obtain CSF.
- Plasma biomarkers taken via venepuncture can be detected with fully automated immunoassays for Aβ, which correlate highly with "gold standard" immunoprecipitation mass spectrometry.
- Development in our understanding of the pathophysiology of AD has led to new drug targets which explore and address other pathological hallmarks of AD.
- Monoclonal antibodies, Lecanemab and Donanemab, have been licenced as a potential for disease modification in AD, although in view of their side effect profile, they have extensive monitoring requirements.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

AS, ALT, EVR and TK designed the work. AS, ALT, and EVR reviewed the literature. AS and ALT drafted the article. TK critically reviewed the article. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final version of the paper. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Professor Tarun Kuruvilla has been an investigator for numerous NIHR portfolio adopted dementia studies as part of his NHS job plan. He is also on the clinical advisory board for Tau Therapeutics. Other authors declare no conflict of interest.

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