Alzheimer's disease

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Abstract | Alzheimer's disease is a chronic illness with long preclinical and prodromal phases (20 years) and an average clinical duration of 8–10 years. The disease has an estimated prevalence of 10–30% in the population >65 years of age with an incidence of 1–3%. Most patients with Alzheimer's disease (>95%) have the sporadic form, which is characterized by a late onset (80–90 years of age), and is the consequence of the failure to clear the amyloid-β (Aβ) peptide from the interstices of the brain. A large number of genetic risk factors for sporadic disease have been identified. A small proportion of patients (<1%) have inherited mutations in genes that affect processing of Aβ and develop the disease at a much younger age (mean age of ~45 years). Detection of the accumulation of Aβ is now possible in preclinical and prodromal phases using cerebrospinal fluid biomarkers and PET. Several approved drugs ameliorate some of the symptoms of Alzheimer's disease, but no current interventions can modify the underlying disease mechanisms. Management is focused on the support of the social networks surrounding the patient and the treatment of any co-morbid illnesses, such as cerebrovascular disease.

Alzheimer's disease is a progressive, unremitting, neurodegenerative disorder that affects wide areas of the cerebral cortex and hippocampus. Abnormalities are usually first detected in the brain tissue that involves the frontal and temporal lobes, and then slowly progress to other areas of the neocortex at rates that vary considerably between individuals (FIG. 1). Alzheimer's disease is associated with the accumulation of insoluble forms of amyloid-β (Aβ) in plaques in extracellular spaces, as well as in the walls of blood vessels, and aggregation of the microtubule protein tau in neurofibrillary tangles in neurons. Aβ is derived by the proteolytic cleavage of amyloid precursor protein (APP) by a complex family of enzymes (γ-secretases and β-secretases), which include presenilin 1 (PS1; encoded by *PSEN1*) and PS2 (encoded by *PSEN2*).

The average duration of illness is 8–10 years, but the clinical symptomatic phases are preceded by preclinical and prodromal stages that typically extend over two decades. Sporadic Alzheimer's disease is the most common type and has a mean age of onset of 80 years. The main cause is the failure to clear Aβ peptide from the brain tissue. However, co-morbidities such as cerebrovascular disease and hippocampal sclerosis are frequent at this age, which complicates diagnosis and management. A family history of affected close relatives is not unusual in sporadic disease, but a small proportion (<1%) of patients have autosomal dominant inherited Alzheimer's disease (DIAD); this form has an early age of onset (mean age of ~45 years). In this subgroup, pathogenetic mutations in the genes encoding APP, PS1 and PS2 are found, which cause overproduction or formation of an aberrant form of Aβ. In most clinical respects, the sporadic and familial forms of Alzheimer's disease are comparable, including the rate of disease progression and biomarker profiles.

As a disease entity, Alzheimer's disease shares many characteristics with other molecularly defined neurodegenerative diseases, such as Parkinson's disease and the frontotemporal dementias. One might, therefore, question whether Alzheimer's disease is an inevitable part of normal ageing or whether it is a discrete disease process. In this Primer, we describe the epidemiology, the molecular mechanisms that underlie the neurodegenerative processes, the diagnosis, screening and prevention strategies that are still in development and current management practices.

Epidemiology

The descriptive (as opposed to analytical) epidemiology of Alzheimer's disease has been the subject of many studies over the past 30 years. Unfortunately, most are of limited value because the confounding variables of co-morbidities (particularly cerebrovascular disease, which is the principal confounding element in descriptive epidemiological studies to date) are often not clearly defined. Although the many descriptive studies of 'dementia' do provide an overall estimate of burden of cognitive impairment in the elderly population, the reported estimates of incidence and prevalence of Alzheimer's disease, as opposed to dementia in general, need to be interpreted with caution. The same problem holds true for putative associations with risk factors. Fortunately, the technologies for specific detection of

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Alzheimer's disease in living patients (as opposed to in post-mortem studies) are now becoming available (including molecular PET imaging and levels of biomarkers — Aβ and tau — in the cerebrospinal fluid (CSF)), which will help to estimate the prevalence and incidence of Alzheimer's disease more accurately.

The best current estimates of the crude annual incidence of sporadic Alzheimer's disease are shown in FIG. 2. The overall mean incidence of 1–3% is consistent with an overall prevalence of 10–30% in the population >65 years of age (given that the mean duration of Alzheimer's disease is 10 years)[1–4]. Few reliable figures of the specific incidence of Alzheimer's disease in people >90 years of age exist, yet this information is crucial to address the question of how Alzheimer's disease relates to the normal brain ageing process. It is often argued that Alzheimer's disease is an inevitable consequence of ageing, and that all people >90 years of age will show evidence of preclinical, prodromal or clinical Alzheimer's disease. However, as seen in post-mortem studies, the prevalence of Alzheimer's disease can taper off at >98 years of age, whereas the prevalence of other neurodegenerative diseases — such as TAR DNA-binding protein 43 (TDP43)-related hippocampal sclerosis — increases[5] (FIG. 3). If this proves correct, it would align Alzheimer's disease with other neurodegenerative conditions, such as Parkinson's disease, which have a clearly definable peak incidence between 70 and 90 years of age, after which a sharp decrement occurs[6–8]. Alzheimer's disease and otherwise non-specified dementia is more prevalent in women than in men; for example, approximately 66% of deaths due to dementia in Australia are women[9]. Whether this is a reflection on higher mortality rates in men from causes other than dementia or Alzheimer's disease is yet to be determined.

Accurately determining the incidence of Alzheimer's disease using new technologies (such as Aβ PET imaging and Aβ levels in the CSF) applied to the methods of analytical epidemiology will be the only way to progress our understanding of 'genes versus environs' in Alzheimer's disease aetiology[10,11]. Current evidence suggests that sporadic Alzheimer's disease occurs at approximately the same rates in all of the world's geographical populations[12]. If confirmed in future studies, this finding will strengthen the argument for genes over environs.

Potentially modifiable risk factors for Alzheimer's disease have been determined, including diabetes mellitus

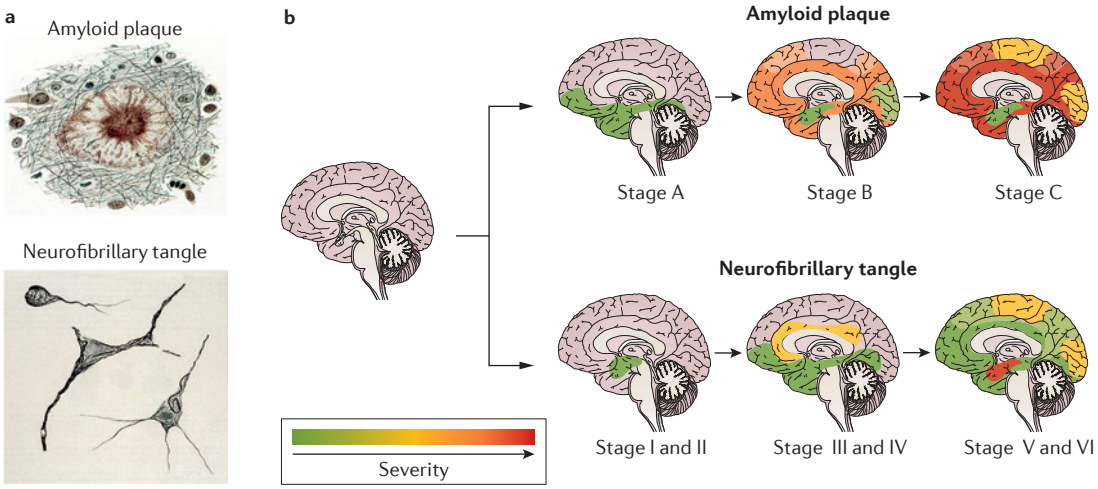

Figure 1 | **The pathological evolution of Alzheimer's disease.** **a** | Amyloid plaques and neurofibrillary tangles spread through the brain as the disease progresses. Images are from Spielmeyer's classic textbook '*Histopathologie des Nervensystems*' using the Bielschowsky method of silver impregnation to visualize the aggregated proteins that constitute the extracellular plaques and intracellular neurofibrillary tangles[172]. **b** | In typical cases of Alzheimer's disease, amyloid-β (Aβ) deposition precedes neurofibrillary and neuritic changes with an apparent origin in the frontal and temporal lobes, hippocampus and limbic system (top row). Less commonly, the disease seems to emerge from other regions of the cerebral neocortex (parietal and occipital lobes) with relative sparing of the hippocampus. The neurofibrillary tangles and neuritic degeneration start in the medial temporal lobes and hippocampus, and progressively spread to other areas of the neocortex (bottom row). With the advent of molecular imaging techniques for Aβ and tau, the longitudinal dispersal of pathological changes will become amenable to real-time *in vivo* study and will not be reliant on post-mortem reconstructions as depicted here. Aβ deposition (stages A, B and C) and neurofibrillary tangles (stages I–VI) are adapted from Braak and Braak[173]. Part **a** adapted with permission from REF. 172, Julius Springer. Part **b** adapted with permission from REF. 173, Elsevier.

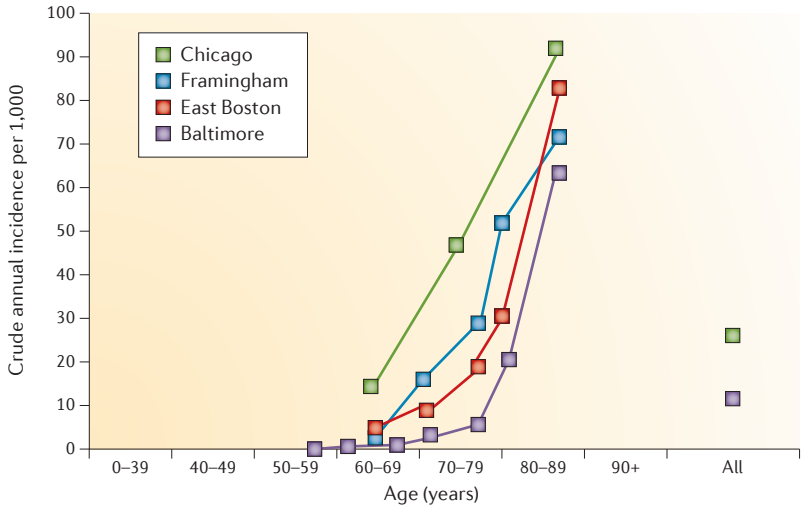

Figure 2 | **The incidence of Alzheimer's disease.** Data from the Framingham[1], east Boston[2], Chicago[3] and Baltimore[4] studies show that the incidence of Alzheimer's disease rises exponentially after the sixth decade of life. These data are based on clinical diagnosis, therefore at least 20% of patients are expected to be misdiagnosed. Improved criteria based on biomarkers (cerebrospinal fluid markers or amyloid-β and tau PET imaging) will lead to more reliable incidence data in the future. Data in patients >90 years of age are limited.

(relative risk (RR): 1.46; 95% CI: 1.20–1.77), mid-life hypertension (RR: 1.61; 95% CI: 1.16–2.24), mid-life obesity (RR: 1.60; 95% CI: 1.34–1.92), physical inactivity (RR: 1.82; 95% CI: 1.19–2.78), depression (RR: 1.65; 95% CI: 1.42–1.92), smoking (RR: 1.59; 95% CI: 1.15–2.20) and low educational attainment (RR: 1.59; 95% CI: 1.35–1.86)[13]. Most of these risk factors are also involved in atherosclerotic cerebrovascular disease. The applicability of each potential risk factor in mitigating the age of onset or severity of Alzheimer's disease progression remains uncertain. In terms of primary and secondary prevention strategies, each of these variables requires further evaluation in properly controlled trials in patients who have been correctly diagnosed as having Alzheimer's disease. Multidomain lifestyle intervention involving diet, exercise, cognitive training and vascular risk reduction, such as the Finnish FINGER study[14], have shown benefit for certain measures of cognition, but do not directly address the issue of whether Alzheimer's disease per se is modifiable or preventable[13,15].

Despite uncertainty over environmental risk factors for sporadic Alzheimer's disease, one key genetic risk factor stands out in all studies: the polymorphism associated with the gene encoding apolipoprotein E (*APOE*) has a major effect in determining the age of onset of Alzheimer's disease. Numerous less frequent and less strongly associated genetic risk factors have been identified in genome-wide association studies and include phosphatidylinositol-binding clathrin assembly protein (*PICALM*), *CD33*, triggering receptor expressed on myeloid cells 2 (*TREM2*), the ATP-binding cassette transporter *ABCA7,* clusterin (*CLU*) and complement receptor type 1 (*CR1*). In addition to *APOE*, many of these genes might play a part in the clearance pathways of Aβ.

Mechanisms/pathophysiology

Studying Alzheimer's disease mechanisms in humans will probably lead to new insights into the pathogenesis, diagnosis and treatment of the disease (TABLE 1). Currently, Aβ, APOE and tau are three elements that have substantial evidence as contributors of Alzheimer's disease. The neuropathological and neurochemical hallmarks of Alzheimer's disease include synaptic loss and selective neuronal death, a decrease in specific neurotransmitters and the presence of abnormal proteinaceous deposits in neurons (known as neurofibrillary tangles) and in the extracellular space (as cerebrovascular, diffuse and neuritic plaques) (FIG. 4).

Aβ in Alzheimer's disease

Several lines of evidence support the notion that Aβ is a pathogenetic peptide in Alzheimer's disease. Aβ — the main constituent of plaques — is cleaved from APP into a heterogeneous group of peptides of varying length (between 38 and 43 amino acids) and slightly different characteristics[16,17]. Furthermore, N-terminally truncated or modified isoforms are found[18]. Proteolytic processing studies have demonstrated that Aβ is a normal product of APP metabolism and is generated at high levels in neurons, but also by other cell types, throughout an individual's lifetime. The neuronal function of APP remains unknown, but it might be involved in synaptic plasticity. Multiple lines of evidence suggest that Aβ accumulation and a change of conformation to forms with a high β-sheet structure is central in Alzheimer's disease pathogenesis[19].

The strongest evidence for the involvement of Aβ in Alzheimer's disease comes from the study of those with the early-onset, inherited form. In more than half of patients with DIAD, mutations in one of three different genes (*APP, PSEN1* and *PSEN2*) are evident[20]. Most mutations result in the overproduction of Aβ — specifically, the 42 amino acid Aβ isoform (Aβ42), which has amyloidogenic characteristics (that is, is more prone to aggregation)[16]. Most mutations in *APP* modify APP processing so that the ratio of Aβ42 to Aβ40 is increased in the plasma of affected patients[21,22]. In addition, mutations in *PSEN1* and *PSEN2* result in increased Aβ42/Aβ40 ratios[23]. The mutation type and associated Aβ42/Aβ40 ratio predict the mean age of onset of dementia, as confirmed in the Dominantly Inherited Alzheimer Network (DIAN) study[24] and a meta-analysis[25]. The increase in the Aβ42/Aβ40 ratio can be detected in the culture supernatants of cells transfected with mutant *APP* or *PSEN1* constructs and in mouse models *in vivo*[21,26]. In addition, the biochemistry of Aβ deposits in 30 DIAD kindreds indicates that all have higher Aβ42 deposition than Aβ40 (REF. 27). Perhaps most relevant, patients carrying these mutations have increased Aβ42/Aβ40 ratios in plasma and increased Aβ42 production in the central nervous system (CNS)[20,28]. Although DIAD is uncommon, the fact that mutations within three different genes lead to similar changes in the ratio of Aβ products suggests that there is a final common pathway in Alzheimer's disease pathogenesis.

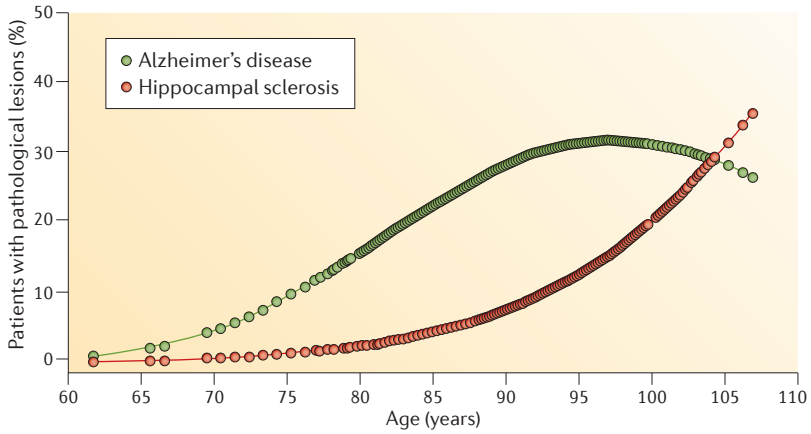

Figure 3 | **Co-morbidities with Alzheimer's disease in advanced ages.** Post-mortem evaluations suggest a trend in which the prevalence of Alzheimer's disease reaches a peak between 95 and 100 years of age and then declines. Conversely, the prevalence of hippocampal sclerosis (as defined by TAR DNA-binding protein 43 (TDP43) immunoreactivity in the neuronally depleted hippocampus) progressively rises with age. If confirmed in future studies, these figures would suggest that Alzheimer's disease is not an inevitable consequence of age per se, which would be consistent with a predominantly genetic aetiology of the disease. Figure from REF. 5. Figure adapted from Nelson, P. T. *et al.*, Hippocampal sclerosis in advanced age: clinical and pathological features, *Brain*, 2011, **134**, 1506–1518, by permission of Oxford University Press.

In addition to the mutations in DIAD, the extra copy of chromosome 21 in those with Down syndrome, which includes *APP,* results in increased Aβ production; these individuals all develop pathological changes that resemble Alzheimer's disease by 35 years of age[29]. In addition, a mutation in *APP* that decreases the production of Aβ has been shown to have remarkable protective effects for late-onset Alzheimer's disease[30].

Human Aβ kinetics: Aβ production, transport and clearance. To understand Aβ kinetics in the pathophysiology of Alzheimer's disease, measurements of labelled proteins in the CNS have been developed[31,32]. The stable isotope labelling kinetics (SILK) technique was used to measure the production and clearance of Aβ in the CNS[31]. Results demonstrated very rapid CSF Aβ kinetics in healthy individuals with an Aβ half-life of approximately 9 hours. Measured effects of drugs that target Aβ generation demonstrated decreases in the production of Aβ[33]. More-recent findings suggest that patients with even very mild sporadic Alzheimer's disease have decreased Aβ clearance in the CNS with no significant difference in average production[32]. The mechanisms underlying this decrease in Aβ clearance remain obscure but could involve APOE and the failure of microglial cells and macrophages to adequately degrade the extracellular Aβ deposits (FIG. 4).

APOE and Alzheimer's disease

APOE on chromosome 19 is the strongest genetic risk factor for developing Alzheimer's disease. APOE is involved in the normal catabolism of triglyceride-rich lipoproteins. One of the first reports linking APOE to Alzheimer's disease pathology was APOE immunoreactivity in Aβ deposits and neurofibrillary tangles, which are hallmarks of Alzheimer's disease pathology[34]. In addition, polymorphisms in the transcriptional regulatory region of *APOE* have been associated with Alzheimer's disease[35].

APOE is a 299 amino acid protein that has three common isoforms in humans that only differ by 1 or 2 amino acids: APOE2 (Cys112 and Cys158), APOE3 (Cys112 and Arg158) and APOE4 (Arg112 and Arg158). The prevalence for each allele is 7% for *APOE2*, 78% for *APOE3* and 15% for *APOE4* in Americans of European descent[36]. The amino acid substitutions affect the total charge and structure of APOE, thereby altering binding to both cellular receptors and lipoprotein particles, and possibly changing the stability and rate of production and clearance. APOE has high expression in the brain, where it is produced primarily by astrocytes and microglia. Under certain conditions, some APOE production can occur in neurons[37]. In the brain, APOE is derived exclusively from within the blood–brain barrier[38] and is present in the CSF at concentrations of approximately 5 μg per ml.

Population studies have demonstrated that *APOE4* increases the risk of developing Alzheimer's disease (one allele imparts a threefold increase in risk and two alleles impart a 12-fold increase in risk)[39] and is also associated with an earlier age of onset of Alzheimer's disease[40,41]. Conversely, *APOE2* decreases the risk of developing Alzheimer's disease[42,43]. The *APOE4* allele has been estimated to contribute to approximately 50% of sporadic Alzheimer's disease[44]. Human APOE isoforms have been shown to cause isoform-dependent decreases (APOE2>APOE3>APOE4) in neuritic plaque load and delayed time of onset of Aβ deposition in several mouse models of Alzheimer's disease[45–48]. Furthermore, human APOE3 decreases Aβ deposition

Table 1 | **Diagnostic and clinical tests for Alzheimer's disease**

Query	Pathogenesis	Pathophysiology	Biomarkers	Pathology	Clinical and cognitive
Assay	Genetic testing of risk factors and protective factors	Aβ, tau and APOE metabolism in the brain, FDG PET and functional connectivity	Biochemical measures in the CSF	Aβ and tau PET imaging, and structural MRI	CDR-SB and neurological examination, and psychometrics
Result	Mutations in *PSEN1*, *PSEN2*, *APP* or *APOE* allele (2, 3 or 4)	Overproduction or impaired clearance of Aβ and aggregation of tau in the brain Hypometabolism in the parieto-occipital cortex	Decreased Aβ42 levels, and increased T-tau and P-tau levels in the CSF	Aβ aggregation, tau aggregation, and hippocampal and cortical atrophy	Memory, attention, executive cognitive dysfunction, functional impairment and dementia staging

Aβ, amyloid-β; APOE, apolipoprotein E; APP, amyloid, precursor protein; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; P-tau, phosphorylated tau; PSEN1, presenilin 1; PSEN2, presenilin 2; T-tau, total tau.

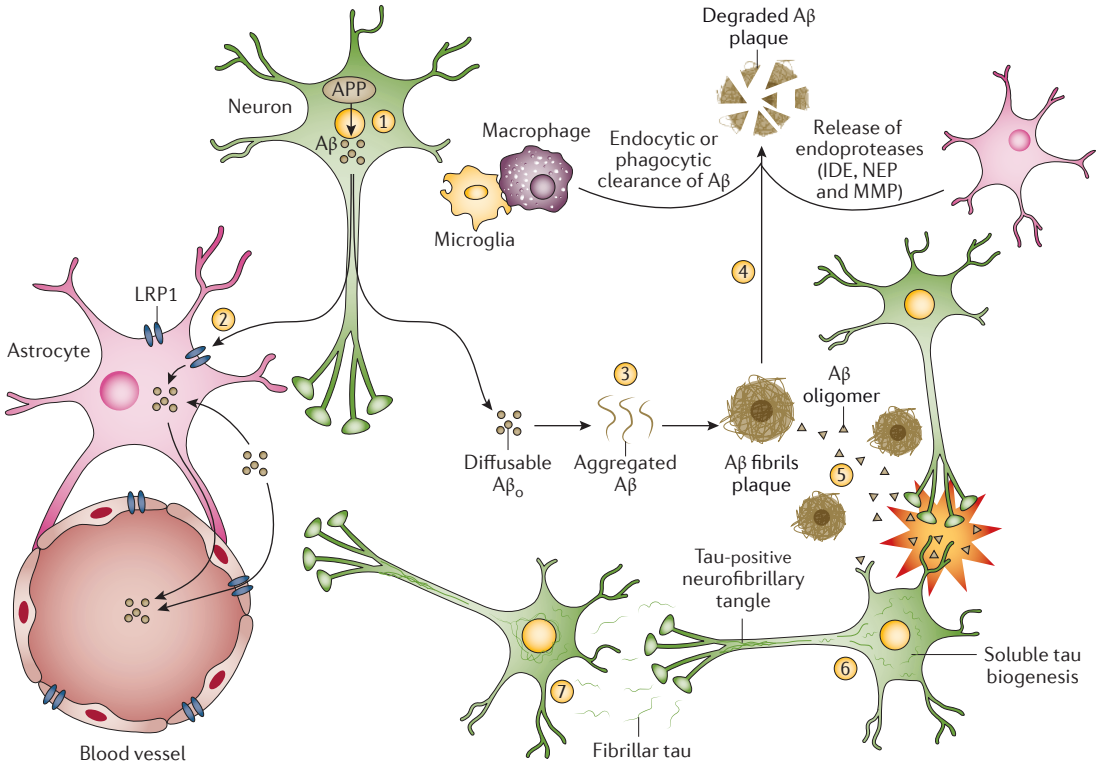

Figure 4 | **Pathways leading to plaques and tangles form the basis of the amyloid-β theory of Alzheimer's disease.** Amyloid-β (Aβ) is cleaved from amyloid precursor protein (APP; step 1) and is released into the extracellular milieu — by a process that is unclear — as diffusible oligomers ($Aβ_o$). $Aβ_o$ can be cleared by mechanisms that involve APOE or can be taken up by astrocytes via low-density lipoprotein receptor-related protein 1 (LRP1; step 2). $Aβ_o$ can also aggregate in the intercellular space to form fibrillary constructs, which in turn assemble into plaques (step 3). Aβ plaques can be cleared from the brain via degradation by endocytic or phagocytic clearance (in macrophages and microglia), or by endoproteases from astrocytes (such as insulin-degrading enzyme (IDE), neprolysin (NEP) and matrix metalloproteinase (MMP); step 4). However, some conformational oligomers that dissociate from Aβ fibrils and plaques may not be cleared and are toxic to adjacent synapses (step 5), and induce tau aggregation by as yet unknown mechanisms. Tau damage occurs in neurons and is mediated by the development of tau-positive neurofibrillary tangles (which extend into the dendrites; step 6). Fibrillar tau can be released and taken up by healthy neurons, triggering tau damage in the uptaking cell (step 7). In addition, Aβ oligomers might drive α-synuclein aggregation in the plaques. Besides Aβ oligomers, mitochondrial damage or dysfunction might also be involved in the neurodegenerative process.

in a dose-dependent manner in mouse models, with the least deposition when two *APOE3* alleles are present[48]. Overall, this indicates that the isoform and amount of APOE in the CNS is crucial for Aβ deposition and neuritic degeneration.

Many studies using cell culture and transgenic animals have investigated the potential mechanisms by which APOE4 may contribute to Alzheimer's disease. These include studies investigating the role that APOE4 has as a pathological chaperone for Aβ, thus affecting the clearance and deposition of Aβ and ultimately contributing to plaque formation[46,49–52]; studies investigating alterations in tau phosphorylation and neurofibrillary tangle formation[49,53]; and studies investigating alterations in lipid metabolism, causing inhibition of neurite extension[54–56]. The APOE4 isoform does not alter Aβ synthesis[50], but can dramatically increase Aβ deposition in animal models of Alzheimer's disease[46]. In accordance, in *ApoE* knock-in mice, clearance of Aβ40 from the CNS to plasma is inhibited in an allele-specific manner (*ApoE4*>*ApoE3* or *ApoE2*), demonstrating the role of APOE in the clearance of Aβ; the capacity of which depends on the isoform[57]. The number of *APOE4* alleles is dose-dependently associated with increased density of Aβ deposits and cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease. APOE is found to be bound to Aβ in biological fluids[58] and is associated with fibrillar Aβ that is found in the brain tissue of patients with Alzheimer's disease. Collectively, these studies indicate that APOE is a major causative or contributing factor for Alzheimer's disease by acting as a chaperone for Aβ, which affects the clearance and deposition of Aβ, ultimately contributing to plaque formation. Any profound change in APOE production and clearance, aspects that are affected differently in the various isoforms, are likely to have a large effect on Aβ deposition and Alzheimer's disease pathogenesis. Thus far, no conclusive evidence for the involvement of APOE4 in tau phosphorylation or lipid metabolism has been found.

Table 2 | **The molecular range of primary and secondary tauopathies***

Pathological diagnosis	T-tau levels (in the CSF)	P-tau levels (in the CSF)‡	Abundant isoform§
Primary tauopathies			
Frontotemporal lobar degeneration associated with *TAU* (also known as *MAPT*) mutations	Normal	Normal P-tau$_{181}$	3R, 3R plus 4R, or 4R
Argyrophilic grain disease	NA	NA	4R
Sporadic multiple system tauopathy	Normal	Normal P-tau$_{181}$	4R
Pick's disease	NA	NA	3R
Progressive supranuclear palsy	Normal	Normal P-tau$_{181}$	4R
Corticobasal degeneration	Normal-to-mild increase	Normal P-tau$_{181}$	4R
Secondary tauopathies			
Alzheimer's disease	Moderate increase	Moderate increase of both P-tau$_{181}$ and P-tau$_{231}$	3R and 4R
Creutzfeldt–Jakob disease	Very marked increase	Normal P-tau$_{181}$ and normal-to-mild increase of P-tau$_{231}$	NA

3R, 3 repeat; 4R, 4 repeat; CSF, cerebrospinal fluid; NA, not analysed (no reliable information available); P-tau, phosphorylated tau; T-tau, total tau. *Tau aggregation and intracellular accumulation occurs either as a primary phenomenon, in which tau lesions are the main pathological feature, or as secondary changes as a consequence of Aβ accumulation (such as in Alzheimer's disease) or PrP^{Sc} (abnormal conformer of the cellular prion protein) deposition (such as in Creutzfeldt–Jakob disease). Curiously, in the secondary tauopathies, T-tau levels are increased in the CSF. ‡Specific post-translational changes of tau (such as phosphorylation on residues 181 and 231 (P-tau$_{181}$ and P-tau$_{231}$, respectively)) vary considerably between these conditions. §There is considerable variation in the relative abundance of the 3R and 4R isoforms of tau; no variation is observed in the other tau isoforms.

Tau: background and significance

Tauopathies, defined as those neurodegenerative diseases with tau aggregation in the brain, are the most common pathological manifestation in neurodegenerative diseases (TABLE 2). The understanding of normal and pathophysiological tau processing in various tauopathies is central to understanding how tau contributes to disease and for the development of tau-targeted therapeutics. Many studies have shown that total tau (T-tau; all tau isoforms irrespective of phosphorylation state) and phosphorylated tau (P-tau; tau with phosphorylation at residues 181 or 231) levels are increased in both the brains and the CSF of patients with Alzheimer's disease[25]. Tauopathies can be classified by the specific tau isoforms that are increased[26–28,30,59] (TABLE 2). However, the mechanism of increased and aggregated tau (that is, whether it is due to increased production or impaired clearance) is not known. Questions about the half-life of tau in the human CNS, whether tau kinetics are altered in Alzheimer's disease and how much tau should be modulated by drugs have not been addressed to date.

Diagnosis, screening and prevention

Diagnosis

Making a diagnosis of Alzheimer's disease on purely clinical grounds is challenging[60], not only in the prodromal stage in which patients only have subtle cognitive symptoms but also in the dementia phase. Indeed, 35% of clinically diagnosed patients with Alzheimer's disease in a large clinical trial had negative Aβ PET scans and were misdiagnosed as having Alzheimer's disease[61]. Co-morbidities such as cerebrovascular disease and hippocampal sclerosis contribute to this difficulty.

Aβ PET imaging. The development of Pittsburgh compound B (PiB) — a radioactive (carbon 11) analogue of the fluorescent amyloid dye thioflavin-T[62] that crosses the blood–brain barrier as well as binds to fibrillar Aβ with high affinity — ushered in the era of *in vivo* Aβ imaging with PET[63–65] (FIG. 5). The past decade has seen studies with PiB contribute substantially to our understanding of the relationship between Aβ deposition and cognitive decline and neurodegeneration in the preclinical, prodromal and dementia phases of Alzheimer's disease[66–68]. These studies have confirmed that Aβ deposition begins decades before dementia and precedes cognitive decline and brain atrophy[69,70], and have established that genetic factors[71] moderate these relationships. In longitudinal studies, Aβ PET is an imaging marker for prediction of progression from mild cognitive impairment to dementia due to Alzheimer's disease[68,72,73]. Aβ PET imaging has made trials in preclinical or asymptomatic patients with Alzheimer's disease feasible[74] and has improved cohort selection for trials in prodromal and mild Alzheimer's disease.

Criteria have been developed for the diagnosis of Alzheimer's disease in the preclinical and prodromal phases of the illness that depend on the demonstration of Aβ accumulation by PET imaging or CSF analysis[75–77]. The presence of a positive Aβ PET scan correlates with low Aβ42 levels in the CSF, and both findings are detectable ≥15 years before the onset of dementia due to Alzheimer's disease[78,79]. Either test can be used to support a diagnosis of Alzheimer's disease, but Aβ PET imaging might be the better method to monitor change in Aβ burden over time and correlates better with the degree of cognitive impairment in the non-demented phase of Alzheimer's disease[80]. Conversely, Aβ42 levels

in the CSF might be more sensitive in the early disease stage[81]. The commercial development of Aβ PET ligands labelled with fluorine-18 now provides the means to diagnose Alzheimer's disease with greater accuracy in the clinic and before the development of dementia[68,82–84]. Comparison of Aβ PET imaging with histopathological analysis in Phase III trials has shown high sensitivity (88–98%) and specificity (88–100%) for the detection of moderate or frequent neuritic Aβ plaques[83–85].

Promising PET ligands for imaging tau aggregates[86] have also been added to large cohort studies of Alzheimer's disease, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), Australian Imaging, Biomarkers and Lifestyle study of ageing (AIBL)[87] and therapy trials. These studies will delineate the relationship of Aβ deposition to tau aggregation and their relative role in cognitive decline and neurodegeneration.

The Alzheimer's disease CSF profile. Brain biochemistry is reflected in the CSF; CSF communicates freely with brain interstitial fluid. CSF collection by lumbar puncture is routine in clinical neurology, and several biomarkers for Alzheimer's disease have been identified, including Aβ42, T-tau and P-tau; the most commonly used assays are specific for P-tau at Thr181 (REF. 88). Knowledge on the mechanisms underlying the change in CSF levels for these biomarkers is essential given that, except for their potential as diagnostic tools, these biomarkers can be applied in clinical studies to explore the molecular disease mechanisms in Alzheimer's disease directly in humans and in clinical trials to identify and monitor the biochemical effects of drug candidates (TABLE 3).

CSF levels of Aβ42 have consistently been found to correlate with post-mortem plaque counts[89] and with amyloid ligand retention on Aβ PET imaging[80,90,91], indicating that this biomarker reflects deposition of the peptide in the brain. CSF levels of T-tau increase not only in Alzheimer's disease but also in neurodegenerative disorders without tau pathology, such as Creutzfeldt–Jakob disease[92], suggesting that T-tau reflects the intensity of neuronal and axonal degeneration in general. Except for tau, there is a general increase in other intracellular neuronal proteins in the CSF of patients with Alzheimer's disease, such as visinin-like protein 1 (VLP1)[93] and neurofilament light polypeptide (NFL)[94], which all predict both the rate of clinical deterioration and the rate of neurodegeneration[91,94]. In addition, the discoveries of tau secretion from cultured cells[95] and mouse neurons[96] raise the question of whether the release of tau from intact neurons into the CSF occurs in humans, but this awaits confirmation. Interestingly, tau secretion would also explain why all healthy young people have measurable tau levels in their CSF. Finally, the CSF levels of P-tau have been shown to correlate with post-mortem measures of neurofibrillary tau pathology[97], with the rate of hippocampal atrophy in the brain[98] and with fast clinical progression[99].

From a diagnostic standpoint, the combination of low CSF Aβ42 levels and high T-tau and P-tau levels is often called the 'Alzheimer's disease CSF profile' and is 85–90% sensitive and specific for Alzheimer's disease, with combined analyses providing better diagnostic performance than any of the CSF biomarkers alone[100,101]. These biomarkers help to differentiate Alzheimer's disease from important differential diagnoses, such as depression and Parkinson's disease, with P-tau levels also providing substantial aid in the differentiation of other dementias, such as frontotemporal lobar dementia and Lewy body dementia[98,102]. The diagnostic performance of these CSF biomarkers has been validated in autopsy-confirmed cohorts[103], with similar or better discriminatory power than in studies based on clinical diagnoses alone.

Considering the high association between CSF Aβ42 and Aβ PET[59,80], with almost identical diagnostic accuracies for the identification of Alzheimer's disease[90], the value of determining CSF tau levels to identify patients with Alzheimer's disease in the prodromal phase might be questioned. However, the main contribution of T-tau and P-tau seems to be in predicting progression. Although Aβ biomarkers — either CSF Aβ42 or Aβ PET — become positive many years before clinical dementia, high CSF T-tau and P-tau levels improve the prediction of progression during a clinically relevant time frame[104–106]. Thus, the updated International Working Group criteria for Alzheimer's disease recommend the algorithm of low CSF Aβ42 levels together with either high T-tau or high P-tau levels for the diagnosis and follow-up of patients with Alzheimer's disease[77].

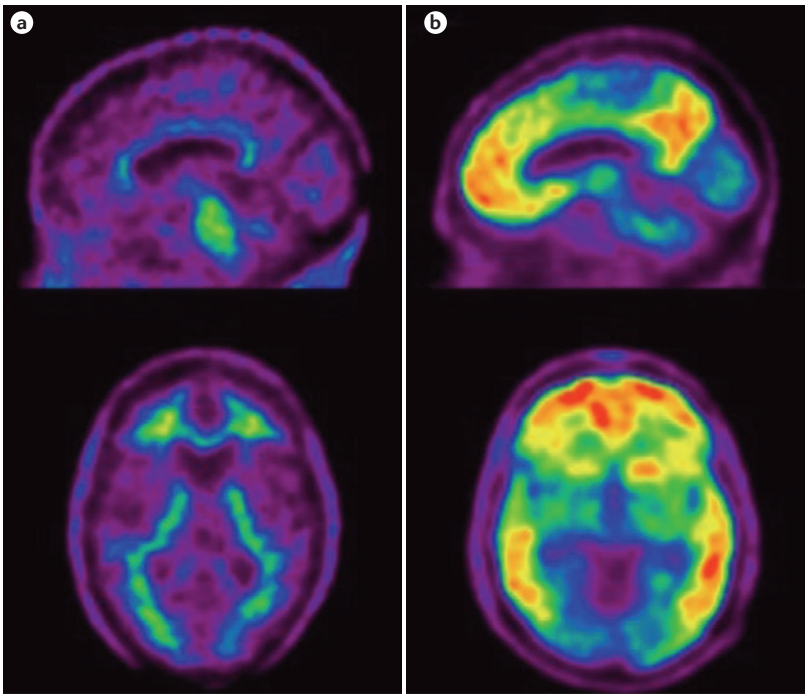

Figure 5 | **Amyloid-β PET imaging.** PET scans for amyloid-β (Aβ) using ^{18}F-NAV4694 PET in two patients with mild cognitive impairment. The scan showed normal, nonspecific white matter binding, and the patient remained stable >4.5 years after the scan (part **a**). The second patient's scan showed extensive binding to Aβ plaques in the frontal, parietal, lateral temporal, posterior cingulate cortex and striatum as typically seen in patients with Alzheimer's disease. The patient progressed to dementia due to Alzheimer's disease 3 years after the scan (part **b**).

In 2003, the first paper on CSF biomarkers in the preclinical phase of sporadic Alzheimer's disease showed a decrease in CSF Aβ42 levels, but not Aβ40 levels, in cognitively normal elderly patients who developed dementia during the 3-year follow-up period[107]. Those with low CSF Aβ42 levels had an eightfold greater risk of dementia, whereas none of the patients with high CSF Aβ42 levels developed dementia. CSF tau levels were not predictive of future dementia in this cohort[107,108]. A later study confirmed that low CSF Aβ42 levels, but not alterations in tau, predicted dementia >8 years before onset[109]. Other studies in the preclinical stage support the notion that baseline CSF Aβ42 levels are a better predictor of future cognitive decline than T-tau or P-tau levels[110,111].

Results from CSF studies in patients with DIAD are somewhat more conflicting. These studies are based on the examination of biomarkers in relation to the estimated age of onset in asymptomatic individuals carrying *APP* or *PSEN1* mutations. The first study found marked increases in the CSF levels of T-tau and P-tau, but no change in Aβ42 levels, in mutation carriers >10 years before the estimated age of onset[112], whereas a larger follow-up study showed marked changes in

Table 3 | **Applications for cerebrospinal fluid biomarkers for Alzheimer's disease**

Principle	Method	Cohort	Biomarkers	Comment
Diagnostics				
Diagnosis of Alzheimer's disease in clinical routine	CSF samples as part of the clinical work-up	Patients with MCI or mild-to-moderate dementia	Aβ42 Aβ42/Aβ40 ratio T-tau P-tau	Aβ42 is the first biomarker that becomes positive during disease progression High T-tau and P-tau levels are more predictive than Aβ42 levels for predicting the progression of cognitive deficits during a clinically relevant time window (1–2 years)
Enrichment of patients with Alzheimer's disease in clinical trials	CSF samples taken during the screening period, before enrolment into a trial*	Phase II and Phase III trials, including patients with early-onset Alzheimer's disease dementia or MCI		
Theragnostics				
Provide evidence of target engagement in humans	CSF samples taken before study initiation, at time points during the trial and at the end of the study Currently, all samples are analysed in one batch at the end of the trial. With technical improvements in assays, it will be possible for real-time evaluations to guide adaptive clinical trial design‡	Phase I trials on healthy volunteers or patients with Alzheimer's disease Phase II and Phase III trials on patients with early-onset Alzheimer's disease dementia or MCI	Aβ42 Aβ40 sAPPβ Aβ oligomers	Amyloid biomarkers may provide evidence for target engagement of an Aβ-specific drug, such as BACE1 inhibitors. Direction of change may depend on the mechanism of action A change in amyloid biomarkers indicates target engagement but does not predict corresponding downstream drug effects or symptomatic effects A change in Aβ oligomers may provide evidence of target engagement for Aβ immunotherapy regimes (in patients with Alzheimer's disease)
Provide evidence of downstream drug effects on neurodegeneration and molecular pathology	CSF samples taken at study initiation and at the end of the study, and if possible at time points during the trial All samples analysed in one batch at the end of the trial‡	Phase II and Phase III trials on patients with early-onset Alzheimer's disease dementia or MCI	T-tau P-tau	Reduction in T-tau levels suggests that the drug affects the intensity of the neurodegenerative process, whereas a decrease in P-tau levels affects tau phosphorylation or possibly tangle formation
			H-FABP VLP1 SNAP25 Neurogranin	Additional biomarkers that reflect neuronal and synaptic degeneration, but are not directly involved in Alzheimer's disease pathogenesis, may provide independent evidence for downstream drug effects
Longitudinal clinical studies				
Examine the temporal evolution of Alzheimer's disease via biomarkers Identify which biomarker changes first during the preclinical phase of Alzheimer's disease and at what time point	CSF samples taken at multiple time points during the study Other Alzheimer's disease biomarkers (MRI measures, and Aβ and tau PET imaging) and cognitive function evaluated at the same visits	Elderly population followed longitudinally until a significant proportion develop cognitive symptoms or dementia	Aβ42 and Aβ40 Aβ oligomers T-tau and P-tau H-FABP and VLP1 SNAP25 and neurogranin Inflammatory and glial biomarkers	These biomarker data will provide information on the time course for, and inter-relation between, pathogenetic events during the preclinical and clinical course of Alzheimer's disease, and how biomarker changes correlate with cognitive deterioration

Note that Aβ-specific clinical trials are used to exemplify the application of CSF biomarkers in clinical trials. Aβ, amyloid-β; BACE1, β-site amyloid precursor protein-cleaving enzyme 1; CSF, cerebrospinal fluid; H-FABP, heart fatty acid-binding protein; MCI, mild cognitive impairment; P-tau, phosphorylated tau; sAPPβ, secreted amyloid precursor protein-β; SNAP25, synaptosomal-associated protein 25; T-tau, total tau; VLP1, visinin-like protein 1. *CSF samples taken for enrichment purposes are analysed directly using stringent laboratory quality control procedures[80]. ‡Paired baseline and end-of-study CSF samples for theragnostics are analysed in one batch at the end of the trial to further minimize analytical variations and possible batch-to-batch differences.

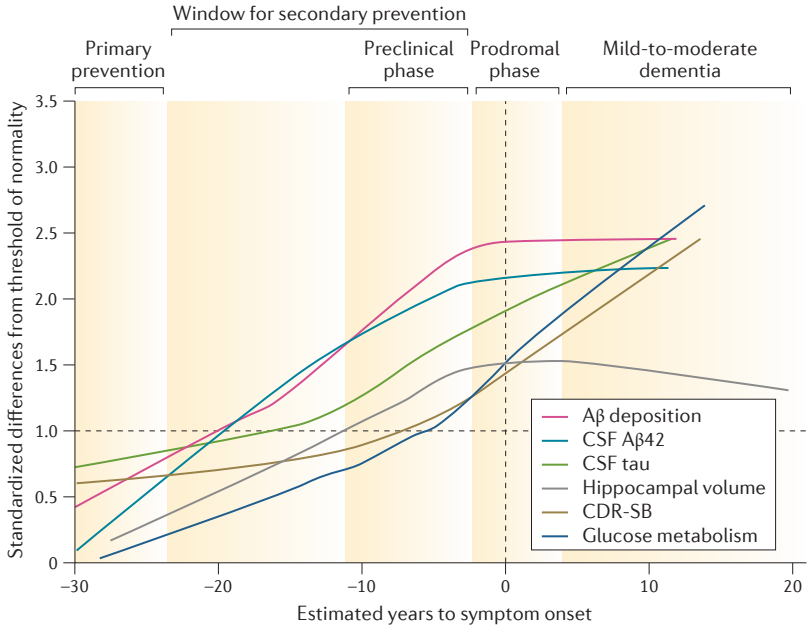

Figure 6 | **Schematic representation of changes in cognitive, metabolic, structural and molecular pathogenetic parameters in relation to estimated years to symptomatic onset of dominantly inherited Alzheimer's disease.** Data based on the Dominantly Inherited Alzheimer Network (DIAN) results[24]. Levels of amyloid-β42 (Aβ42) in the cerebrospinal fluid (CSF) can be elevated 30 years before symptom onset, and cross the threshold of normality (defined as 1 standard deviation above the normal value) at 20 years before symptom onset. These CSF changes are closely matched by Aβ PET increases, and are followed by CSF tau increases crossing the threshold 15 years before symptom onset. Structural changes reflecting synaptic loss, such as hippocampal atrophy, become apparent 10 years before symptom onset. Cognitive changes (assessed using the Clinical Dementia Rating-Sum of Boxes (CDR-SB)) and impaired glucose metabolism become abnormal relatively late in the natural history, being detected approximately 5 years before symptom onset. Similar relationships are found in those with sporadic Alzheimer's disease[69].

CSF levels of Aβ42, T-tau and P-tau, as long as 17 years before the estimated age of onset[113]. These results were supported in a study from the DIAN project, showing significant changes in CSF levels of both Aβ42 and T-tau 10–15 years before the estimated age of onset in mutation carriers[24]. In that study, onset was estimated as the difference between the age of the participant and the age of parental symptom onset[24]. In addition to CSF biomarkers, clinical, cognitive and imaging changes in studies from the DIAN project were examined, and curves were fitted to the DIAN cross-sectional data (FIG. 6). Clinical impairments as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SB) were observed and were found to start approximately 6 years before the estimated symptom onset. Mutation carriers showed volume loss in the hippocampus 10 years before estimated symptom onset. Decreased cerebral glucose metabolism was detected in the precuneus approximately 5 years before the estimated symptom onset. Measures of fibrillar amyloid deposition were increased in the precuneus of mutation carriers 20 years before the estimated symptom onset and further increased with decreasing estimated age of onset. Curve fits have suggested that mutation carriers exhibit high levels of CSF Aβ42 at least 30 years before the estimated symptom onset, which might then decrease and pseudo-normalize approximately 20 years before symptom onset; low levels would be evident about 15 years before the estimated symptom onset. CSF tau levels are increased approximately 15 years before the estimated symptom onset.

Overall, abnormalities in biomarker measurements can be detected 15–20 years before the estimated onset of clinical symptoms. The predicted differences in clinical, cognitive, structural, pathological and biochemical DIAD measures are similar to measures of sporadic Alzheimer's disease[69,114,115], suggesting a common pathophysiology between sporadic Alzheimer's disease and DIAD. Indeed, treatment trials in patients with DIAD are likely to be translatable to the much more common sporadic Alzheimer's disease, at least the effect on specific pathological changes such as Aβ deposition, while the effect on progression of cognitive symptoms may be more variable in sporadic disease given the higher age of patients who often have multiple co-morbidities that contribute to the clinical symptoms[116].

Extended clinical studies with multiple longitudinal biomarker assessments are therefore needed to identify when during the preclinical evolution of the different biomarkers change from normal and which biomarkers change first. Such longitudinal clinical biomarkers studies including neuropsychological evaluations, Aβ PET imaging and MRI measurements, and also using novel biomarker modalities such as tau PET[117] and CSF biomarkers for synaptic function and degeneration[118,119] will add to the understanding of the evolution of pathogenic processes during the course of Alzheimer's disease.

Diagnostic CSF biomarkers are increasingly used for theragnostics (TABLE 3), that is, pharmacodynamic tools to prove target engagement and to identify and monitor downstream effects of drug candidates[88,120]. β-site APP-cleaving enzyme 1 (also known as β-secretase 1 (BACE1)) inhibitor treatment might serve as an example in which CSF Aβ fills a role to verify preclinical data of target engagement, that is, reduced Aβ levels in the CSF when BACE1 inhibitor therapy is effective. As proof of principle, a short-term Phase I trial in a limited number of healthy volunteers was conducted and showed marked and sustained reduction in the levels of Aβ40 and Aβ42 in the CSF accompanied by a decrease in secreted APPβ (sAPPβ) with BACE1 inhibitor therapy, thereby verifying target engagement[121].

Finally, downstream biomarkers could be used in Aβ-specific clinical trials to identify drug effects downstream of the primary target of the drug (TABLE 3). Reductions towards normalization in CSF levels of neuronal and synaptic biomarkers, such as tau and neurogranin, might indicate that a drug slows down the rate of progression of neuronal and synaptic degeneration. However, no robust or consistent change in CSF Aβ levels have been found[122], but CSF P-tau levels were reduced in Phase II[123] and Phase III[61] testing of the humanized Aβ-specific monoclonal antibody bapineuzumab.

Aβ42 and Aβ40 can also be measured in the plasma, but at much lower levels than in the CSF. However, results from studies examining plasma Aβ levels from

a diagnostic standpoint show consistent change and a broad overlap with cognitively normal elderly[124]. This is probably because a substantial proportion of plasma Aβ comes from peripheral tissues and thus does not accurately reflect brain Aβ metabolism or pathology[125].

Prevention

Enabled by recent advances in biomarkers and neuroimaging, the field of Alzheimer's disease has moved to secondary prevention trials in the preclinical stages of Alzheimer's disease, aimed at slowing the disease process in the brain and preventing the progression of the clinical manifestations. Convergent data from both genetic-at-risk and age-at-risk cohorts strongly suggest that the pathophysiological process of Alzheimer's disease begins more than a decade before the clinical stage of dementia[24,75,126]. Given the evidence that Aβ accumulation is an early upstream initiator of the disease process, our best opportunity for intervention with Aβ-specific therapies could be before clinically evident symptoms[127]. Fortunately, several secondary prevention trials have been recently launched, and additional trials are being planned to test Aβ-specific monoclonal antibodies (solanezumab[128], gantenerumab[129] and crenezumab[130]). For example, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) study is a 3-year, Phase III, secondary prevention study of an Aβ-specific monoclonal antibody (solanezumab) in clinically normal older individuals with evidence of increased Aβ accumulation on screening using Aβ PET imaging[74]. The primary outcome is a cognitive composite[131] with several novel secondary clinical outcomes, including computerized testing with CogState platform (Cogstate Ltd, Melbourne, Australia) and participant-reported outcomes[132], as well as biomarker and neuroimaging exploratory outcomes. In addition, the A5 trial that will test a BACE inhibitor in a similar cohort is currently being planned.

The DIAN Trials Unit (DIAN-TU) is currently testing two Aβ-specific monoclonal antibodies (solanezumab and gantenerumab) in a Phase II secondary prevention trial in presymptomatic individuals with *PSEN1*, *PSEN2* and *APP* mutations, and is planning to add more therapeutic arms to the study[133]. The DIAN-TU is using an adaptive trial design based on biomarker and imaging outcomes, and will advance promising treatments into a Phase III trial with cognitive and clinical outcomes.

Table 4 | **Characteristics of current treatments of Alzheimer's disease**

Agent	Formulation	Dose	Regimen and titration schedule	Indication
Cholinesterase inhibitors				
Donepezil	Tablet	5 mg or 10 mg	Begin with 5 mg daily and advance to 10 mg daily after 4–6 weeks	Mild-to-moderate Alzheimer's disease
	Tablet	10 mg	Once daily	Moderate-to-severe Alzheimer's disease
	Orally disintegrating tablet	5 mg or 10 mg	Once daily	Mild-to-moderate Alzheimer's disease
	Orally disintegrating tablet	10 mg	Once daily	Moderate-to-severe Alzheimer's disease
	Tablet	23 mg	Advance to this dose after 3 months at 10 mg daily	Moderate-to-severe Alzheimer's disease
Rivastigmine	Capsule	1.5 mg, 3 mg, 4.5 mg or 6 mg	Begin with lowest dose twice daily and increase at 2-week intervals to highest dose	Mild-to-moderate Alzheimer's disease
	Patch	4.6 mg or 9.5 mg	Begin with a 4.6-mg once daily patch; advance to 9.5 mg daily	Mild-to-moderate Alzheimer's disease
	Patch	13.3 mg	Advance to this dose after 1 month at 9.5 mg daily	Severe Alzheimer's disease
Galantamine	Tablet	4 mg, 8 mg or 12 mg	Advance from lowest to highest dose twice daily at 4-week intervals	Mild-to-moderate Alzheimer's disease
	Solution	4 mg	Advance from 4 mg to 12 mg twice daily at 4-week intervals	Mild-to-moderate Alzheimer's disease
	Extended-release capsule	8 mg, 16 mg or 24 mg	Advance from lowest to highest dose once daily at 4-week intervals	Mild-to-moderate Alzheimer's disease
NMDA receptor antagonist				
Memantine	Tablet	5 mg or 10 mg	Advance from 5 mg daily to 5 mg twice daily, to 10 mg in the morning and 5 mg in the evening, to 10 mg twice daily	Moderate-to-severe Alzheimer's disease
	Solution	2 mg per ml	Advance from 2.5 ml to a total of 5 ml twice daily in 2.5-mg increments at 1-week intervals	Moderate-to-severe Alzheimer's disease
	Extended-release capsule	7 mg, 14 mg, 21 mg or 28 mg	Advance from lowest to highest dose daily at 1-week intervals	Moderate or severe Alzheimer's disease

NMDA, *N*-methyl-D-aspartate.

Table 5 | **Characteristics of medical foods available for patients with Alzheimer's disease**

Medical food	Constituents	Potential mechanism of action	Adverse effects
Vayacog®	A combination of phosphatidylserine and omega-3 fatty acids	Provides lipids that are essential for cell membrane fluidity and structure, especially of neurons	Indigestion and other gastrointestinal symptoms
Souvenaid® (REF. 175)	Omega-3 fatty acids, choline, uridine monophosphate, antioxidants and B vitamins	Support synaptic function	Indigestion and other gastrointestinal symptoms
CerefolinNAC®	Vitamin B12, vitamin B6, vitamin B2 and L-methylfolate	Prevent vitamin B12 and folate deficiencies, which are associated with cognitive disorders, neuroinflammation and oxidative stress	Indigestion and other gastrointestinal symptoms
Axona®	Fractionated coconut oil (caprylic triglyceride (a medium chain triglyceride))	Alternative energy source to compensate for the reduced ability to use glucose in the brains of patients with Alzheimer's disease	Diarrhoea

The Alzheimer's Prevention Initiative (API) is currently testing another Aβ-specific monoclonal antibody (crenezumab) in the Colombian PS1 kindred (a very large extended pedigree with the E280A mutation in *PSEN1*) in a biomarker and clinical outcome trial[134]. The API has also announced plans for two trials in individuals who are homozygous for *APOE4* to test a BACE inhibitor and an active vaccine against Aβ. The TOMMORROW trial aims to use a different mechanism: either lowering glucose metabolism or inhibiting peroxisome proliferator-activated receptor-γ using pioglitazone in asymptomatic older individuals who carry the high-risk *TOMM40* allele (closely linked, if not synonymous with, the *APOE4* allele)[135].

It is likely that combination therapy targeting multiple mechanisms might be needed even in the preclinical stages of Alzheimer's disease, as a substantial proportion of asymptomatic individuals with evidence of Aβ accumulation also show evidence of neurodegeneration[136]. Of course, the ultimate goal would be primary prevention — that is, prevention of the accumulation of Aβ and tau aggregates, synaptic dysfunction and neuronal loss. To achieve this goal, therapeutic intervention might need to be started by middle-age. Very long-term treatment with monoclonal antibodies is unlikely to be practical; however, an active immunization strategy beginning at 50 years of age with booster injections is likely to be cost effective. Although evidence suggests that late-onset Alzheimer's disease is more likely to be related to failure of clearance of Aβ rather than overproduction[32], decreasing Aβ production before any accumulation would possibly be an effective primary prevention strategy, which is supported by the recent report of a protective mutation in the BACE cleavage region of APP[30].

Management

The management of Alzheimer's disease involves a complex interaction between the clinician, the patient, the patient's caregiver and the health care system in which the care is delivered. Non-pharmacological management involves caregiver education or use of behavioural techniques to optimize patient–caregiver interactions and minimize behavioural disturbances. Pharmacological management includes cognition-enhancing agents, treatment of behavioural abnormalities that can arise during the course of Alzheimer's disease and medical management of commonly encountered systemic disorders or complications of Alzheimer's disease. Given that medical foods and nutritional supplements form an important part of social management of patients and their family, we discuss them here as part of a management strategy. Exercise and lifestyle-related issues are included in comprehensive recommendations. Attending to the needs of the caregiver is a crucial component of the management of Alzheimer's disease. Successful management can help the patient to remain at home for a longer period of time, minimize cognitive and functional decline, optimize behaviour and improve caregiver quality of life.

Cognition-enhancing agents

Owing to the nonspecific degeneration caused by the accumulation of Aβ, many types of neurotransmitter abnormalities have been reported, affecting cholinergic, monoaminergic and glutamatergic systems[137]. Two classes of cognition-enhancing drugs have been approved for use in Alzheimer's disease — cholinesterase inhibitors and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine (TABLE 4). Cholinesterase inhibitors decrease the extrasynaptic metabolism of acetylcholine, increase the synaptic residence time of the neurotransmitter and enhance postsynaptic stimulation. Preserved postsynaptic cholinergic mechanisms translate the augmented signal into cognitive and behavioural effects. Cholinesterase inhibitors include donepezil, rivastigmine and galantamine. Donepezil and galantamine are acetylcholinesterase inhibitors, and rivastigmine is a dual acetylcholinesterase and butyrylcholinesterase inhibitor[137]. Galantamine has nicotinic as well as muscarinic cholinergic properties. Common adverse effects of cholinesterase inhibitors include diarrhoea, nausea, vomiting, bradycardia, muscle twitching and nightmares. Resting bradycardia is a contraindication of cholinesterase inhibitors. Cholinesterase inhibitors should also be used with caution in individuals with a history of gastrointestinal disturbances. Anticholinergic agents should not be used in patients receiving cholinesterase inhibitors, and the combination of two or more cholinesterase inhibitors has not been studied and should be avoided.

Table 6 | **Drugs commonly used for behavioural changes in Alzheimer's disease**

Neuropsychiatric disorder	Drug class	Examples	Adverse effects	Refs
Agitation and/or psychosis	Antipsychotic agents	Risperidone Quetiapine Dextromethorphan plus quinidine*	Twofold increase in mortality	176–178
Depression	SSRIs and SNRIs	Citalopram	Effectiveness not always confirmed in RCTs	179
Apathy‡	CNS stimulants	Methylphenidate	Generally well tolerated	180
Sleep disturbances	Non-benzodiazepine hypnotics	Zolpidem	Generally well tolerated	181
	Antidepressant agent	Trazodone	Generally well tolerated	181

None of the listed agents are approved for these indications; all use of psychotropic agents for these conditions in patients with Alzheimer's disease is off-label. Antipsychotic agents have a 'black box' warning regarding increased mortality when used in patients with dementia. Examples given in the table are chosen to represent members of classes of agents; other agents may be equally effective. Comparative information is not available. CNS, central nervous system; RCT, randomized controlled trial; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor. *Combined dextromethorphan plus quinidine is approved for treatment of pseudobulbar affect in patients with dementia. ‡Apathy is only treated when severe.

Memantine acts on the glutamatergic system by occupying and antagonizing the NMDA receptor, thereby normalizing neurotransmitter abnormalities observed in Alzheimer's disease[138]. Adverse effects of memantine include dizziness, headache and lethargy. Combination therapy with a cholinesterase inhibitor and memantine is common and provides additive benefits[139]; a fixed-dose combination of the two agents is available (Namzaric™, Actavis (Dublin, Ireland) and Adamas Pharmaceuticals Inc. (Emeryville, California, USA)). Observational data indicate moderate stabilization of disease course in patients receiving combination therapy[140]. Combination therapy is generally well tolerated.

The magnitude of the clinical response to be expected from cognitive enhancers of either chemical type is limited. A minority of patients experience cognitive improvement, as demonstrated on clinical rating scales and sometimes observed by the family of the patient. A majority of patients experience a delay of decline with a deferral of additional loss of cognition for 6–9 months following introduction of therapy[141,142]. Long-term studies suggest continued benefit from therapy despite the patient's decline, with less impairment observed in treatment groups than in those not receiving treatment. Switching from one cholinesterase inhibitor to another is prompted by adverse effects, uninterrupted cognitive decline, or patient or caregiver preference. Termination of therapy is typically decided on after negotiation between the clinician and the family of the patient when the patient has reached a level of impairment at which cognition-enhancing therapy no longer produces an impact on quality of life.

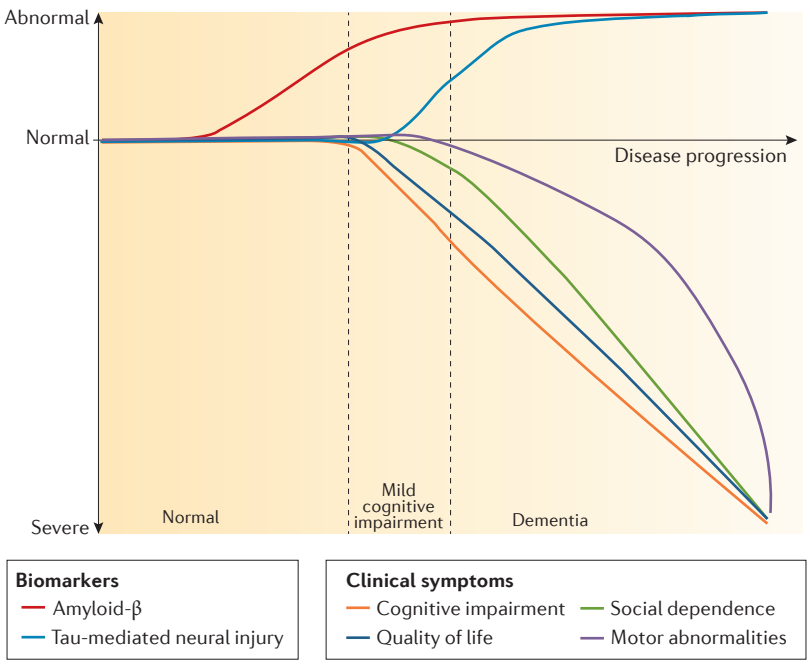

Figure 7 | **Quality of life of patients with Alzheimer's disease.** Schematic depiction of relative rates of change of cognitive impairment, social dependence and motor abnormalities that adversely affect the general quality of life in people who develop dementia due to Alzheimer's disease.

Medical foods

Medical foods are available for the management of Alzheimer's disease (TABLE 5). Medical foods are generally regarded as second-line approaches to Alzheimer's disease management for patients who are not responding adequately to pharmacotherapy, are intolerant to cholinesterase inhibitors or memantine and when families want to pursue therapeutic options beyond approved drug treatments[143]. These foods are not subject to the same rigorous testing in randomized controlled trials that are required for regulatory approval of a drug. According to the US FDA, a medical food is defined as 'a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation' (REF. 144). Medical foods are mainly used for

nutritional purposes; proof of efficacy of medical foods for improving cognition, function or behaviour is not required. One medical food, CerefolinNAC® (Pamlab Inc., Covington, Louisiana, USA), also has a specific use in lowering serum homocysteine levels[145].

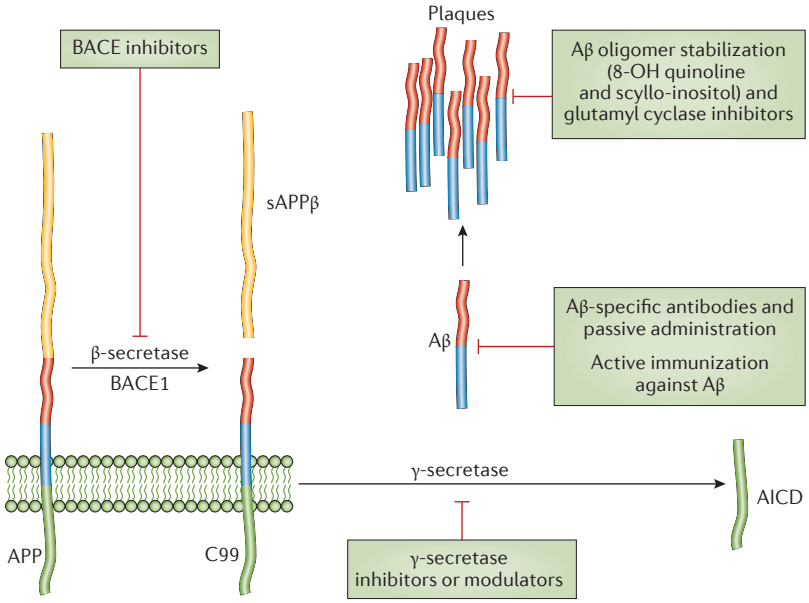

Figure 8 | **Potential strategies to manipulate amyloid-β in Alzheimer's disease.** Amyloid-β (Aβ) can be targeted by the passive administration of Aβ-specific monoclonal antibodies (TABLE 7). In addition, several active immunization protocols with different Aβ fragments are under investigation including: Aβ1–42 (ANI1792 (Janssen, Pfizer and Elan)), which had toxic adverse effects (vasculitis); Aβ (V950 (Merck); no data available); Aβ1–6 B cell epitope (CAD106 (Novartis); Alzheimer Prevention Initiative, combination therapy with β-site amyloid precursor protein-cleaving enzyme 1 (also known as β-secretase 1 (BACE1)) inhibitor); AD02/04 (AFFiRiS AG) Aβ1–6 mimetic (not effective, but response has been seen in those receiving adjuvant alone); Aβ1–15 palmitoylated liposome (ACI–24 (AC Immune)); Aβ1–14 (UB-311 (United Biochemical, Inc.), T helper cell strategy); and Aβ1–12 triplicate combined with a T helper cell strategy (Lu AF20513 (Lundbeck and Otsuka)). Several randomized clinical trials on BACE1 inhibitors are ongoing. Most seem to substantially lower the levels of Aβ in the cerebrospinal fluid (CSF). Other drugs include: MK-8931 (Merck; EPOCH and APECS trials (Phase II and Phase III, respectively)); AZD3293 (AstraZeneca and Eli Lilly; AMARANTH trial (Phase II and Phase III)); E2609 (Eisai and BIIB (Biogen Idec; Phase II)); JNJ-54861911 (Johnson and Johnson (Phase II)); and BI-1147560 (Boehringer Ingelheim (Phase I)). Some γ-secretase inhibitors and modulators have been trialled (semagacestat (Eli Lilly) and avagacestat (Bristol-Myers Squibb)) and were found not to be efficacious and are toxic. Other current Phase II studies that target Aβ include: PBT2 (Prana Biotechnology), which induces Aβ oligomer stabilization or neutralization of toxic properties and might also permit increased catabolism; PQ912 (ProBiodrug AG), a glutamyl cyclase inhibitor of Aβ3(pE)-42 (pyroglutamate) formation; and ELND005 scyllo-inositol (Transition Therapeutics Inc.), which inhibits Aβ oligomer aggregation and prevents binding of Aβ oligomers to cell membranes. Other current Phase III trials include: LMTX™ (TauRx), a nonspecific protein aggregant inhibitor (which primarily targets tau); pioglitazone (Takeda and Zinfandel; the TOMORROW trial), a peroxisome proliferator-activated receptor-γ (PPARγ) agonist; masitinib (AB Science), a tyrosine kinase inhibitor; idalopirdine (Lundbeck and Otsuka), a 5-hydroxytryptamine receptor 6 (5-HT6) antagonist; encenicline (FORUM Pharmaceuticals), a nicotinic acetylcholine receptor subunit α7 (α7-nAChR) agonist; brexpiprazole (Lundbeck and Otsuka), a dopamine D2 receptor agonist; nilvadipine (Archer Pharmaceuticals), a calcium channel blocker; and SB-742457 (Roivant Neurosciences), a 5-HT6 antagonist. 8-OH, 8-hydroxy; AICD, amyloid precursor protein intracellular domain; APP, amyloid precursor protein; sAPPβ, soluble amyloid precursor protein-β. Figure from REF. 174, Nature Publishing Group.

Nutritional supplements

Oxidative injury by free radicals is a postulated mechanism by which protein aggregates injure cell membranes during the course of Alzheimer's disease[17,146,147]. Epidemiological evidence suggests that individuals with diets high in antioxidants have lower rates of developing Alzheimer's disease[146,147]. High-dose vitamin E (2,000 IU daily) has been shown to slow functional decline in some randomized controlled clinical trials[146], but not in others[147]. Adverse cardiac events observed with vitamin E supplementation have limited the use of this approach[148]. Antioxidants such as omega-3 fatty acids, curcumin, coenzyme Q10 and vitamin C are often given to patients with Alzheimer's disease. However, evidence of efficacy of antioxidant supplementation in patients with Alzheimer's disease is limited[149].

Treatment of neuropsychiatric disturbances

Agitation, psychosis with delusions and hallucinations, depression, apathy and sleep disturbances are all commonly encountered in patients with Alzheimer's disease[150]. Neuropsychiatric symptoms impair quality of life for the patient and their caregivers, contribute to functional dependence and hasten residential placement[151,152]. In some cases, the severity of symptoms is sufficient to require pharmacological intervention. TABLE 6 provides a summary of neuropsychiatric abnormalities that frequently emerge during the course of Alzheimer's disease and examples of psychotropic agents that are used to ameliorate the behavioural changes. No drugs are approved by the FDA specifically for the treatment of behavioural changes in patients with Alzheimer's disease.

Choosing to treat neuropsychiatric symptoms is based on the clinician's view of the possible benefit and potential harm[153]. Best practices for clinical use of psychopharmacological agents in Alzheimer's disease include: defining the target symptoms, starting with low doses unless symptoms are very distressing for the patient and caregiver (higher doses might be required early if patients are very disturbed or aggressive); advancing the dose until symptoms are controlled or adverse effects emerge; limiting the duration of treatment as much as possible; and re-instituting therapy if symptoms recur with dose reductions. Vigilance about adverse effects, education of patients and caregivers about neuropsychiatric symptoms and their treatment, and management of possible adverse effects related to treatment are important.

Care of the caregiver

Alzheimer's disease strikes families, not individuals, and addressing the needs of the patient's family is essential to optimize the quality of life of the affected person and their caregiver. Behavioural and functional disturbances have greater impact on quality of life of patients and caregivers than cognitive decline[154]. Interventions that engage both patients and family members provide caregivers with support, problem-solving abilities, technical skills, home modification strategies, and referral to community resources help to maintain the family in their role as caregivers and enable patients to remain at home for longer periods of time[155].

Table 7 | **Passive administration of amyloid-β-specific monoclonal antibodies**

Drug	Mechanism of action	Phase	Cohort	Outcome
Bapineuzumab ('bapi'; developed by Elan, Janssen and Wyeth (Pfizer))	Targets N-terminal epitope (537-Å^2-buried surface area) of Aβ in α-helical conformation; envelops extreme N-terminal by capping it. Binds to fibrillar (plaque and perivascular) more than soluble oligomeric or monomeric species of Aβ	Phase III	*n* = 2,500 Mild-to-moderate clinically diagnosed patients with Alzheimer's disease 71–76 weeks	15–20% incidence of ARIA-E (dose related) Aβ PET substudy: 30–40% of recruits fell below cut-off, suggesting clinical misdiagnosis; Aβ PET- positive patients showed 25% slowing of Aβ PET change in treatment over placebo CSF substudy: no change in Aβ levels, decrease in tau levels and plasma Aβ levels were not reported No cognitive benefit Drug development ceased in 2012
Aducanumab (BIIB 037; developed by Biogen Idec)	Binds to the N terminus of Aβ in an extended conformation (different from bapi) Reacts with aggregated rather than monomeric Aβ species in a naturally occurring epitope or conformation Derived from human auto-antibody clone Very high half-life *in vivo*	Phase Ib	*n* = 194 Prodromal-to-mild Alzheimer's disease defined by Aβ PET imaging 26 and 54 weeks	Manageable dose-dependent increased incidence of ARIA-E, especially in *APOE4* carriers Aβ PET imaging (florbetapir): significant dose-dependent reduction at 26 and 54 weeks Significant slowing in cognitive decline (assessed using the MMSE and CDR-SB) at 52 weeks with highest dose Moving into Phase III
Gantenerumab (developed by Roche)	Targets Aβ1–11 N-terminal epitope in linear extended conformation (larger than bapi and longer than aducanumab)	Phase III	*n* = 799 Mild or moderate clinically diagnosed patients with Alzheimer's disease	Aβ PET imaging: small substudy; reduction at higher dose Trial halted with interim futility analysis Another Phase III study (*n* = 1,000) in progress in patients with mild Alzheimer's disease and preclinical DIAD (DIAN-TU)
Solanezumab ('sola'; developed by Eli Lilly)	Targets mid-region Aβ16–23 with picomolar affinity: an atypically large epitope (960 Å^2) involving deeply buried Phe–Phe dipeptide core that is buried early in oligomeric assembly, but is available in monomeric structures, as the structure is an intermediate between α-helical and β-sheet forms	Phase III	*n* = 2,000 Mild-to-moderate clinically diagnosed patients with Alzheimer's disease 80 weeks	Safe and well tolerated; a low (1%) incidence of ARIA-E Aβ PET imaging substudy: 30% of recruits fell below cut-off; no effect of drug on SUVR CSF substudy: increase in total Aβ levels and decrease in free Aβ40 levels; no change in tau levels. Plasma: substantial increase in total Aβ levels and 'plaque-specific' fragments, which are not normally detected in plasma Overall, no cognitive benefit but small and significant 30–35% slowing of cognitive decline (assessed by the ADAS-cog and MMSE) in mild cases Extension study results provide evidence for disease modification; further Phase III trials are in progress (assessing preclinical, prodromal and mild Alzheimer's disease)
Crenezumab (developed by Genentech, a member of the Roche group)	Targets mid-region Aβ16–23 (the same epitope as sola but with significantly lower affinity (in the low nanomolar range))	Phase II	*n* = 444 Mild-to-moderate clinically diagnosed patients with Alzheimer's disease 72 weeks	Safe and well tolerated; a low incidence of ARIA-E Aβ PET imaging (florbetapir) substudy: no effect CSF substudy: Aβ levels increased; plasma Aβ levels were not reported Cognitive benefit seen in milder cases Extension study ongoing. Currently in trials in preclinical DIAD (assessing the E280A mutation in *PSEN1*)
BAN 2401 (developed by Eisai and Biogen Idec)	Targets Aβ epitope (soluble 'protofibrillar' oligomers)	Phase II	*n* = 800 18 months	Trial in progress
Other antibodies against Aβ (Eli Lilly, AstraZeneca, Sanofi, Acumen, Janssen, Pfizer and GlaxoSmithKline)		Phase I or Phase II		Trials in progress

Aβ, amyloid-β; ADAS-cog, Alzheimer's Disease Assessment Scale-cognition; APOE4, apolipoprotein E4; ARIA-E, vasogenic oedema and sulcal effusions; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CSF, cerebrospinal fluid; DIAD, autosomal dominant inherited Alzheimer's disease; DIAN-TU, Dominantly Inherited Alzheimer Network-Trials Unit; MMSE, Mini-Mental State Examination; PSEN1, presenilin 1; SUVR, standard uptake values ratio.

Patients with advanced-stage disease

All patients with mild and moderate Alzheimer's disease progress to advanced-stage disease unless they succumb to co-morbid age-related illnesses. Patients with Alzheimer's disease are subject to cardiovascular disease, stroke, cancer and other age-associated conditions that can shorten their lifespan and the duration of Alzheimer's disease. Eye disease and hearing problems can lead to social isolation. Patients who survive into advanced phases of the illness are vulnerable to urinary tract infections associated with incontinence, aspiration pneumonia that reflects impaired swallowing, and decubitus ulceration of the skin related to diminished mobility and unrelieved pressure on skin around bony prominences, such as the vertebra, hip and pelvic structures, heels and elbows.

Caregivers must be vigilant about hydration and nutrition in advanced phases of the illness. Oral care and prevention of dental caries are often overlooked and must be supervised by caregivers. Palliative care and treatment of pain is crucial to patient comfort and quality of life in advanced phases of the disease[156]. Armed with knowledge of diverse management strategies and the intent to preserve the personhood of patients who are cognitively impaired, the clinician can have a substantial effect on care of patients with advanced-stage Alzheimer's disease.

Quality of life

Measurement of quality of life has special challenges in Alzheimer's disease[157] (FIG. 7). Insight is impaired by the disease from the earliest stages; patients underestimate their memory loss, do not recognize their own cognitive disabilities and overestimate their quality of life compared with how others view their circumstances[158,159]. Family members rate the quality of life of the patient as worse than that perceived by the patient and the gap widens as dementia progresses[160]. Patient mood and the presence of depression is consistently related to decreased quality of life for patients with Alzheimer's disease, whereas burden, behavioural disturbances and cognitive impairment are determinants of the caregivers' view of the patient's quality of life[159,161]. Quality of life of caregivers is markedly affected by Alzheimer's disease. The main contributors include patient behavioural disturbances and dependency, caregiver isolation, poor quality of the premorbid relationship with the patient and lack of resources[162]. Among behavioural changes, both agitation and depression contribute considerably to diminished quality of life for the caregiver[163,164].

Improving quality of life has had limited success. Quality of life has diverse determinants with many contributing factors, such as financial resources, and partner's relationship with the patient are unlikely to be affected by an intervention[165]. Showing an improvement in quality of life is further complicated by the lack of insight into compromised quality by the patient and the possible exaggeration of poor caregiver estimates of patient quality of life by caregiver depression or frustration. Despite these challenges, some interventions have improved quality of life, including delayed functional loss (such as daily activities) in patients with cholinesterase inhibitors[166], reduced caregiver distress with decreased patient agitation[167], and improved caregiver quality of life and delayed residential placement of patients with educational interventions[168]. Together, these studies show that expert management of patients with Alzheimer's disease and attention to the caregivers can improve quality of life.

Preliminary investigations have begun to explore the effect of knowledge of the risk of developing Alzheimer's disease on the well-being of patients. Revealing *APOE* carrier status in the context of genetic counselling did not increase depression or suicidality[169]. Most research physicians think that biomarker status (that is, Aβ PET imaging) should be revealed to individuals when those data become available in the course of research[170].

Outlook

Steady incremental progress is being made in understanding the natural history of Alzheimer's disease, particularly the kinetics of evolution of the disease and its interaction with co-morbidities (especially cerebrovascular disease) and normal brain ageing.

Many genetic risk factors for sporadic Alzheimer's disease are known; the main factor is the *APOE4* allele, which might predict the rate of clearance of Aβ from the brain. As a strong risk factor for Alzheimer's disease, APOE represents a potential target for future disease-modifying therapies. By elucidating how metabolism of APOE is controlled in the human CNS, and how the APOE isoforms differ, we will potentially enhance insight into the pathophysiology of Alzheimer's disease, which might ultimately lead to improved treatments. Other genetic risk factors seem to modulate the processing of Aβ, and their interactions with the effect of APOE will contribute to the development of prognostic algorithms. Refinements in predictive algorithms that also use CSF and PET markers of preclinical, prodromal and clinical stages of Alzheimer's disease should improve their reliability and increase their applicability in diagnosis and prognosis.

As yet, targeting the tau pathway in Alzheimer's disease has proven intractable, which might be attributable to a failure of understanding the relationship between Aβ and tau. Quantitative measurement of the physiological and pathological tau will be crucial for understanding the pathogenesis of Alzheimer's disease and other tauopathies. For example, we need to know why tau is increased in the CSF of patients with Alzheimer's disease — either by overproduction or impaired clearance — to guide therapeutic targeting. By quantifying the changes in tau production and clearance, better estimates of target engagement can be made.

Despite many disappointing clinical trial outcomes, knowledge gained in tackling the underlying disease mechanisms will enable future disease-modifying strategies to emerge. The increasing number of trials on drug candidates targeting Aβ[61,128,171] has put focus on the need of biomarkers to improve diagnostic accuracy and to optimize the chance of identifying clinical benefits of the tested drug candidate (FIG. 8;TABLE 7).

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Author contributions

Introduction (C.L.M.); Epidemiology (C.L.M.); Mechanisms/pathophysiology (R.B.); Diagnosis, screening and prevention (K.B., C.C.R. and R.A.S.); Management (J.L.C.); Quality of life (J.L.C.); Outlook (C.L.M.); Overview of the Primer (C.L.M.).

Competing interests

C.L.M. has provided consultation to Eli Lilly, Actinogen and Prana Biotechnology. He has stock ownership in Prana Biotechnology. R.B. has provided consultation to FORUM, Merck, Roche, Sanofi, Boehringer Ingelheim and Eli Lilly. He currently consults and owns stock in C2N Diagnostics, which he co-founded. He also receives research support from Eli Lilly, Roche, Merck and the Dominantly Inherited Alzheimer Network (DIAN) Pharma Consortium (comprising Amgen, Biogen Idec, Eisai, FORUM, Genentech, Janssen, Lilly, Roche and Sanofi). K.B. has served on advisory boards for Amgen, Eli Lilly, IBL International, Novartis, Roche Diagnostics and Sanofi-Aventis. C.C.R. has received research grants from GE Healthcare, Avid Radiopharmaceuticals, Primal, AstraZeneca and Navidea in the past 2 years. R.A.S. has served as a consultant for Janssen, Genentech, ISIS Pharmaceuticals and Roche. She receives research support from Eli Lilly and Janssen. J.L.C. has provided consultation to AbbVie, Acadia, Actinogen, ADAMAS, Alzheon, Anavex, Avanir, Biogen Idec, Biotie, Boehinger Ingelheim, Chase, Eisai, FORUM, Genentech, Grifols, Intracellular Therapies, Eli Lilly, Lundbeck, Merck, Neurotrope, Novartis, Nutricia, Otsuka, Pfizer, Resverlogix, Roche, Roivant, Suven, Takeda and Toyoma companies.