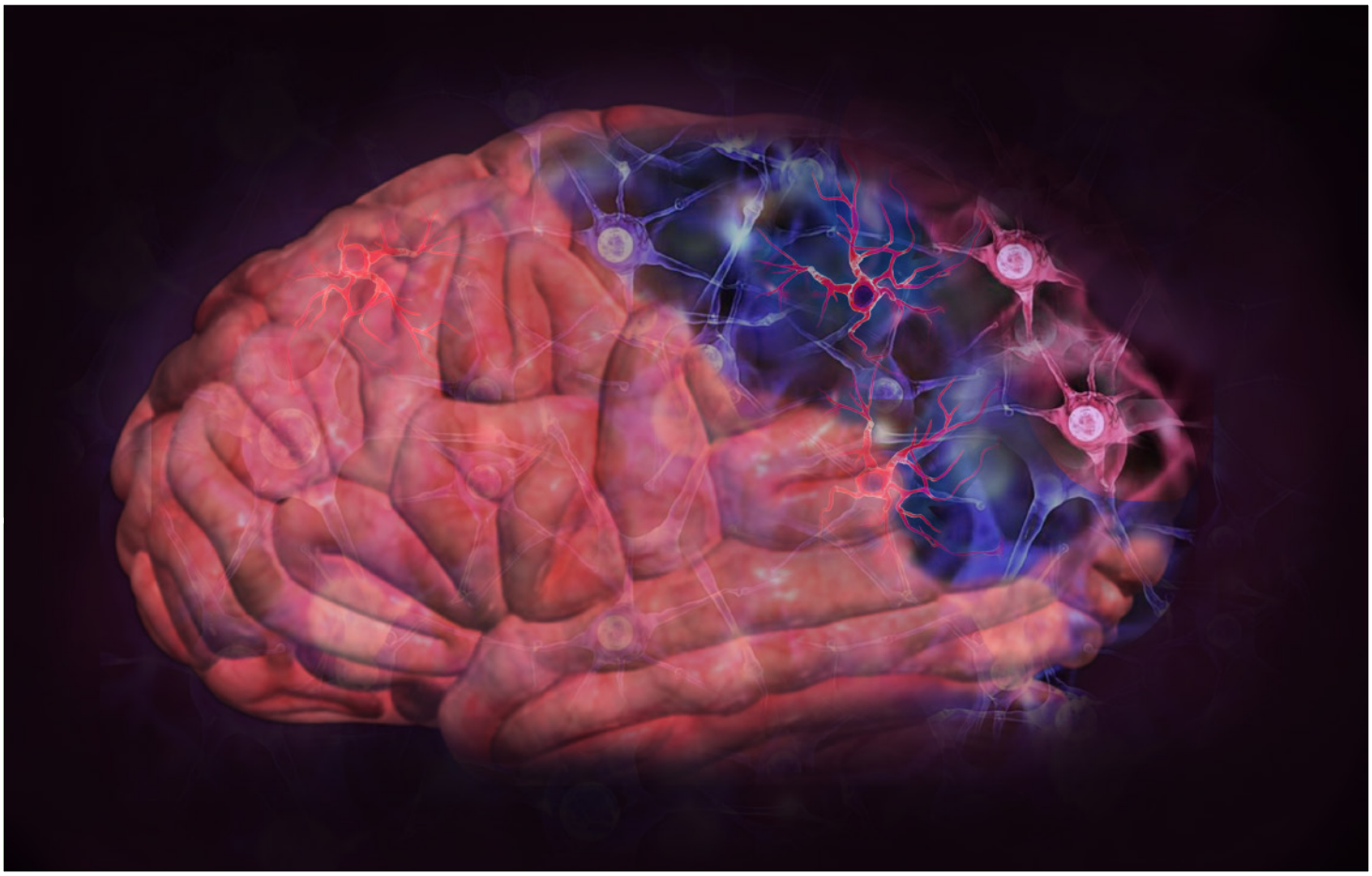

Alzheimer's Disease: Diagnosis And Management Updates

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Alzheimer's Disease: Diagnosis And Management Updates

ANCC Accredited NCPD Hours: 2.5hrs

Target Audience: RN/APRN

Need Assessment

Alzheimer's disease diagnosis and treatment has seen significant improvement in recent decades due to advancement in detection of biomarkers and clinical response models developed in recent years. This article discusses the development of standardized methods for clinical tests, magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebrospinal fluid (CSF) biomarkers from multicentre trials. CSF biomarkers are largely consistent with disease trajectories predicted by β-amyloid cascade. Brain atrophy and hypometabolism levels show predicted patterns but exhibit differing rates of change depending on region and disease severity. There are new recommendations in assessment and diagnostic categorization along with the development of blood biomarkers that are potentially non-invasive and low-cost alternatives to CSF biomarkers for the early detection of Alzheimer Disease.

Objectives

- Describe the Benefits of Cholinergic Therapies at Various Stages of Alzheimer's Disease
- Discuss the Diagnosis of Alzheimer's Disease in Primary Care
- Identify the various factors Influencing Diagnosis of Alzheimer's Disease
- Describe the Neural Cognitive Effects of Anticholinergic Therapies in Alzheimer's Disease
- Discuss the Protective Effects of Treatment for Alzheimer's Disease in Primary Care

Goal

The goal of this article is to discuss the development of methods for the early detection of Alzheimer's disease. The article also discusses the efforts involved in the management of this clinical condition based on emerging evidence.

Introduction

Alzheimer's disease (Alzheimer Disease) is a progressive neurodegenerative disease with a complex and heterogeneous pathophysiology. The number of people living with Alzheimer Disease is predicted to increase; however, there are no disease-modifying therapies currently available and none have been successful in late-stage clinical trials. ***Biomarkers measured in cerebrospinal fluid (CSF) or blood hold promise for enabling more effective drug development and establishing a more personalized medicine approach for Alzheimer Disease diagnosis and treatment.*** Biomarkers used in drug development programmes should be qualified for a specific context of use (COU). These ***COUs include,*** but are not limited to, subject/patient selection, assessment of disease state and/or prognosis, assessment of mechanism of action, dose optimization, drug response monitoring, efficacy maximization, and toxicity/adverse reactions identification and minimization.

The core Alzheimer Disease ***CSF biomarkers*** (As shown in fig:1) ***Aβ42, t-tau, and p-tau are recognized by research guidelines*** for their diagnostic utility and are being considered for qualification for subject selection in clinical trials. However, there is a need to better understand their potential for other COUs, as well as identify additional fluid biomarkers reflecting other aspects of Alzheimer Disease pathophysiology. Several novel fluid biomarkers have been proposed, but their role in Alzheimer Disease pathology and their use as Alzheimer Disease biomarkers have yet to be validated. [1, Rank 5

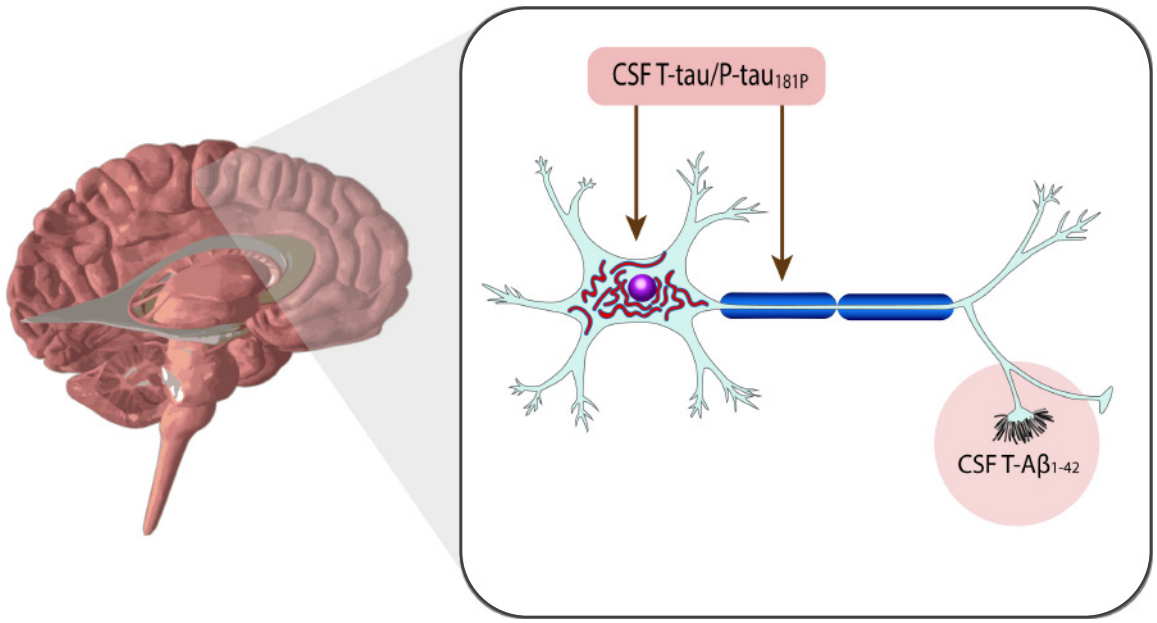

Figure 1 : CSF biomarkers in Alzheimer Disease

" These Context of use include, but are not limited to, subject/patient selection, assessment of disease state and/or prognosis, assessment of mechanism of action, dose optimization along with drug response monitoring, efficacy maximization, and toxicity /adverse reactions identification and minimization "

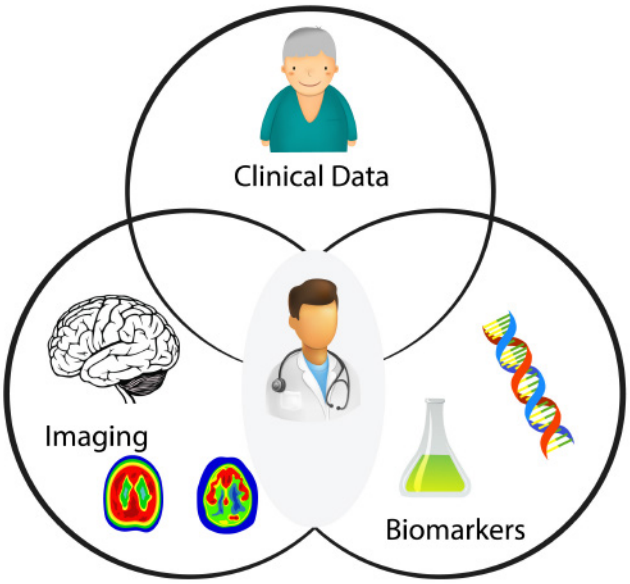

Figure 2 : Diagnosis of Alzheimer's disease

Diagnosis of Alzheimer's Disease in Primary Care

Late-onset Alzheimer's disease dementia, the most prevalent age-related neurodegenerative disease, is clinically characterized by a progressive loss of memory and other cognitive functions.(As shown in fig:3)

In contrast to early-onset autosomal dominant forms of Alzheimer's disease, which are directly linked to abnormalities of amyloid-β, the cascade of pathophysiological events that leads to late-onset Alzheimer's disease is not yet fully understood. ***Contemporary evidence suggests that late-onset Alzheimer's disease is a complex polygenic disease that involves aberrant interaction among several molecular pathways. By definition, age is the strongest risk fac-***

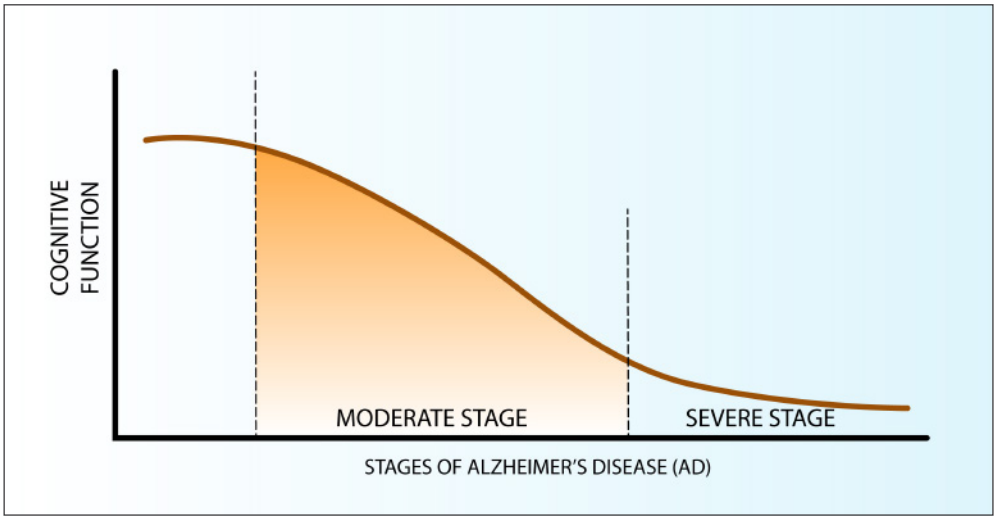

Figure 3 : graphical representation of relation between change in the cognitive function and progression of Alzheimer's disease

tor(As shown in fig:4), ***and probably also cardiovascular and lifestyle risk factors.***

The neuropathological features (As shown in fig:4) of Alzheimer's disease include the accumulation of several abnormal proteins such as amyloid-β in plaques and hyperphosphorylated-tau in neurofibrillary tangles.

manifestations. In recent years, however, failure of clinical trials in Alzheimer's disease has been the rule rather than the exception, and no new drugs for Alzheimer's disease have been approved by the US Food and Drug Administration (FDA). The multifaceted, heterogeneous, progressive, and interactive pathophysiology

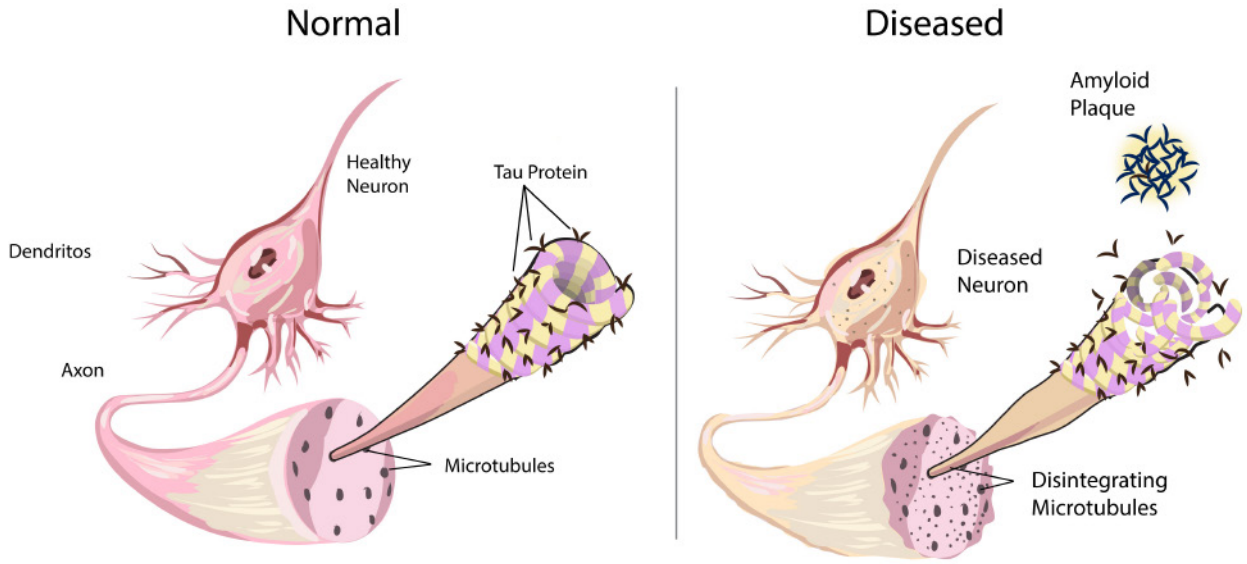

Figure 4 : Neuro-pathological features of Alzheimer's disease

This leads to massive loss of synapses, dendrites, and eventually neurons. Clinical expression of the disease reflects the dysfunction and eventual failure of both neurochemical and structural neural networks, including the 'cholinergic system'(As shown in fig:6). Although the pivotal events in the pathogenesis of Alzheimer's disease are not fully understood, several competing theories on the underlying biology of the neurodegeneration have guided research into interventions to modify, arrest, or delay the progression of the disease and its clinical

of Alzheimer's disease also suggests a likely need for ***individualized combination treatments that may need to be varied from one stage of the disease to another, and perhaps also from one patient to another.*** [5, Rank 2]The cholinergic hypothesis revolutionized the field of Alzheimer's disease research by ***transporting*** it from the realm of ***descriptive neuropathology to the modern concept of synaptic neurotransmission.*** It is based on ***three milestones:***

1) The discovery of depleted presynaptic cholinergic markers in the cerebral cortex.

2) The discovery that the nucleus basalis of meynert (nbm) in the basal forebrain is the source of cortical cholinergic innervation that undergoes severe neurodegeneration in Alzheimer's disease.

3) The demonstration that cholinergic antagonists impair memory whereas agonists have the opposite effect. The hypothesis received compelling validation when cholinesterase inhibitor therapies were shown to induce significant symptomatic improvement in patients with Alzheimer's disease.

Although other relevant pathophysiological mechanisms have received more research attention in recent years, treatments that improve cholinergic function remain critical in the management of patients with Alzheimer's disease. [7, Rank 2]

Benefits of Cholinergic Therapies at Various Stages of Alzheimer's Disease

Cholinergic synapses are ubiquitous in the human central nervous system. Their high density in the thalamus, striatum, limbic system, and neocortex suggest that cholinergic transmission is likely to be critically important for memory, learning, attention and other higher brain functions. Several lines of research suggest ***additional roles for cholinergic systems in overall brain homeostasis and plasticity. As such, the brain's cholinergic system occupies a central role in ongoing research related to normal cognition and age-related cognitive decline, including dementias such as Alzheimer's disease.*** The cholinergic hypothesis of Alzheimer's disease centres on the progressive loss of limbic and neocortical cholinergic innervation. Neurofibrillary degeneration in the basal forebrain is believed to be the primary cause for the dysfunction and death of forebrain cholinergic neurons, giving rise to a widespread presynaptic cholinergic denervation. ***Cholinesterase inhibitors increase the availability of acetylcholine at synapses in the brain and are one of the few drug therapies that have been proven clinically useful in the treatment of Alzheimer's disease dementia, thus validating the cholinergic system as an important therapeutic target in the disease.*** This review includes an overview of

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the role of the cholinergic system in cognition and an updated understanding of how cholinergic deficits in Alzheimer's disease interact with other aspects of disease pathophysiology, including plaques composed of amyloid-β proteins. [2, Rank 3]

Factors Influencing Diagnosis of Alzheimer's Disease in Primary Care

In contrast to M1 receptors, which are mostly preserved, there is a loss of cortical nicotinic receptors. Postsynaptic nicotinic receptor enhances the neuronal firing rates contributing to the hippocampal long-term potentiation, a neuronal-level component of learning and memory. The application of cholinergic agonists and antagonists to hippocampal slices has clarified the role for acetylcholine in long-term potentiation. Therefore, ***altered patterns of nicotinic and muscarinic receptor distribution in Alzheimer's disease are likely to influence many functions of the cerebral cortex and limbic areas through perturbations of synaptic physiology.***

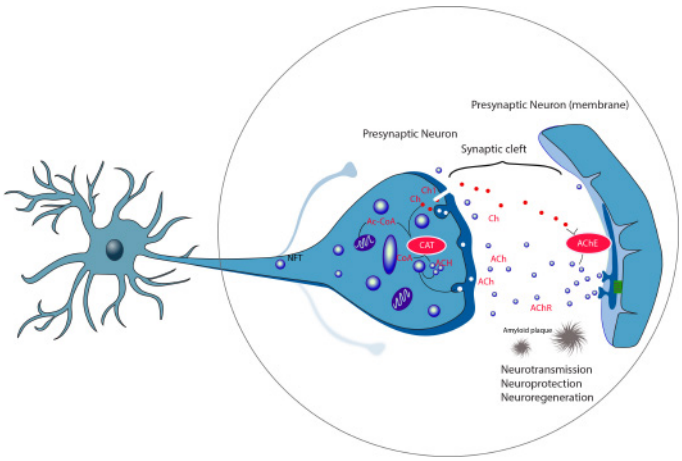

Figure 5 : Normal synaptic physiology

An upregulation of cortical choline acetyltransferase neuronal expression has been shown in prodromal Alzheimer's disease patients, suggesting that such neurochemical events may compensate for the depletion of basal cholinergic neurons. Moreover, it has been shown that Alzheimer's disease patients have higher levels of nicotinic gene expression compared to healthy controls. The influence of these dynamic changes upon Alzheimer's disease pathogenesis remains to be elucidated. [6, Rank 3]

There is also evidence implicating acetylcholine in a variety of essential functions that promote experience-induced neuroplasticity, the synchronization of neuronal activity, and network connectivity. For instance, variable stimulation of

the Nucleus Basalis of Meynert , an acetylcholine-rich area of the basal forebrain with wide projections to the cortex, has been shown to produce extensive cortical remodelling and to modulate cortical sensory maps. Through intrinsic (Nucleus Basalis of Meynert) and extrinsic perivascular postganglionic sympathetic nerve innervation, the cholinergic system has also been shown to promote cerebral vasodilation and perfusion. In studies, electrical and chemical stimulation of cholinergic neurons in the Nucleus Basalis of Meynert results in a significant increase in cerebral blood flow in several cortical areas. In addition to disrupting synaptic transmission in cortex and limbic areas, the cholinergic lesion of Alzheimer's disease may therefore also interfere with multiple aspects of neuroplasticity and with cerebral haemodynamic processes. [4, Rank 3]

" Cholinergic lesion of Alzheimer's disease may also interfere with multiple aspects of neuroplasticity and with cerebral haemodynamic processes. "

" Evidence implicating acetylcholine in a variety of essential functions that promote experience-induced neuroplasticity, the synchronization of neuronal activity, and network connectivity "

Neural Cognitive Effects of Anticholinergic Therapies in Alzheimer's Disease

The negative pharmacological effects of anticholinergic drugs on human memory and learning have been reported, and more recent data support these observations. The use of anticholinergic medications in non-demented older adults has been associated with significantly slower reaction times on a measure of rapid information processing and lower cognitive test scores. Moreover, the increased use of anticholinergic medications was correlated with reduced cognitive function in a systematic review of studies performed in older adults. The cumulative effect of anticholinergic drugs has also been associated with poorer cognitive abilities, as well as poorer functional outcomes (i.e. activities of daily living) in cohort studies of older populations. Furthermore, a recent meta-analysis demonstrated that the exposure of older adults with cardiovascular disease to anticholin-

ergic drugs was associated with an increased risk of cognitive impairment. In that study, a greater burden of anticholinergic exposure was shown to more than double the odds of all-cause mortality. [10, Rank 1]

Recent data also suggest that the negative cognitive effects of cumulative anticholinergic drugs in older adults may not be transient. Among cognitively healthy individuals in the Alzheimer Disease Neuroimaging Initiative and Indiana Memory and Aging Study, the participants who had been regularly taking one or more medications with medium or high anticholinergic activity prior to study entry demonstrated worse immediate recall and executive function than the participants who were not actively using anticholinergic medications at study entry. Strikingly, cognitively normal adults taking anticholinergic medication were observed to have reduced total cortex volume, increased bilateral lateral ventricle volume, and increased inferior lateral ventricle volume.

In addition, across both groups of participants, there was a significant longitudinal association between anticholinergic use and later progression to mild cognitive impairment (MCI) or Alzheimer's disease dementia. Concordantly, in a prospective population-based cohort study of participants ≥65 years with no dementia at study entry, greater cumulative use of anticholinergic drugs over 10 years was linked to a statistically increased risk for incident dementia and for Alzheimer's disease specifically. Thus, higher estimates of cumulative exposure to anticholinergic therapies were associated with a greater risk for incident dementia or Alzheimer's disease dementia. In addition to these findings, doses of anticholinergic medication appear to unmask signs of impending dementia in individuals with preclinical Alzheimer's disease. In a study of healthy older adults at risk for Alzheimer's disease, single-dose administration of the anticholinergic drug scopolamine unmasked cognitive deficits and poorer cognitive performance more often in patients with higher brain amyloid-β burden on PET images. [9, Rank 4]

Protective Effects of Treatment for Alzheimer's Disease in Primary Care

Treatment that promotes cholinergic function in individuals with, or at risk for, Alzheimer's disease may also have more durable beneficial biological effects on the brain than a temporary augmentation of cognitive function. The Hippocampus Study Group found, in a placebo-controlled trial in people with suspected prodromal Alzheimer's disease, that use of the cholinesterase inhibitor 'donepezil' was associated with substan-

tially less regional cortical thinning and basal forebrain atrophy over time. A placebo-controlled study on the same population found a 45% reduction in the rate of hippocampal atrophy after 1 year of treatment with donepezil, a finding previously reported by another research group investigating patients with fully expressed dementia.

Although these results have not yet been linked to a specific biological mechanism, they raise the possibility of substantial brain structural protective effects of cholinergic treatment during various stages of Alzheimer's disease(As shown in fig:6).

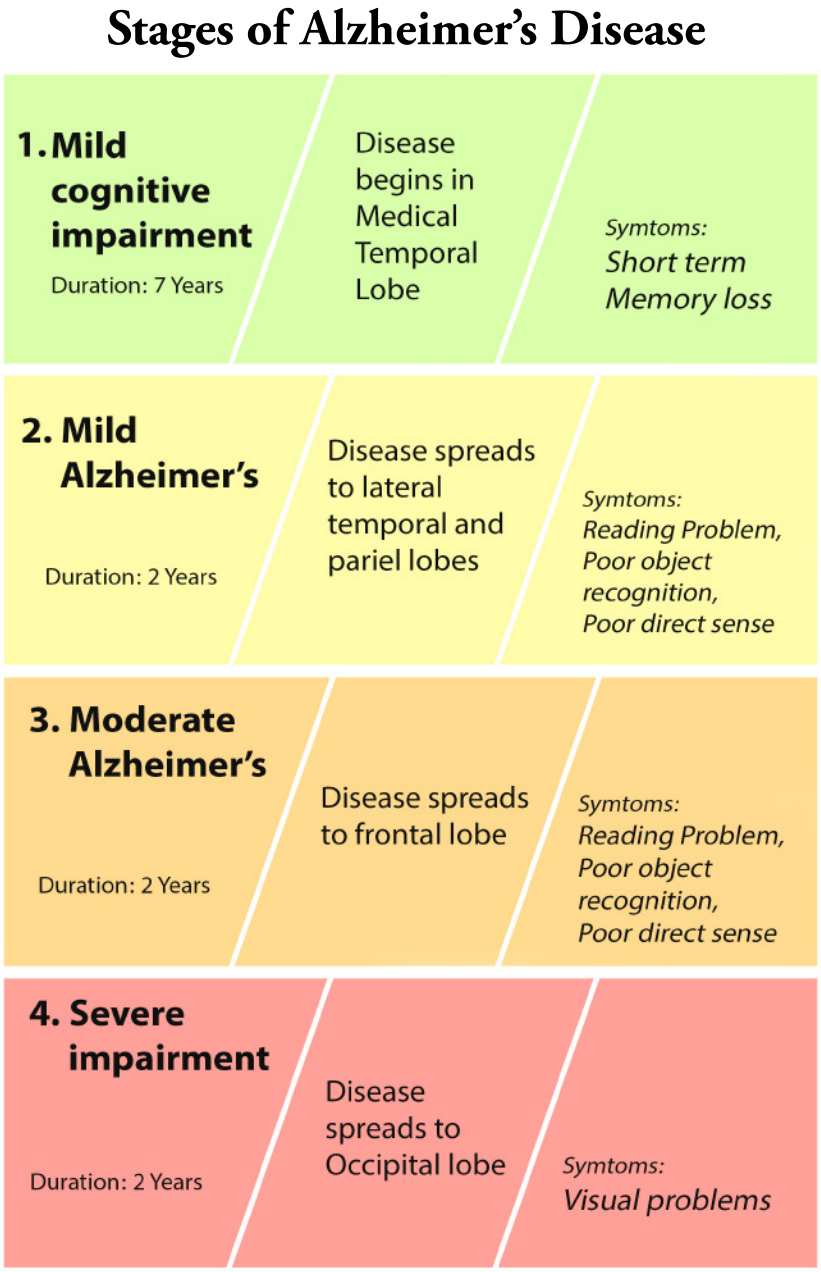

Figure 6: Stages of Alzheimer's disease

Several studies have also explored the role of cholinesterase inhibitors on cerebrovascular perfusion in Alzheimer's disease and other dementias. Patients with Alzheimer's disease dementia receiving a single dose of cholinesterase inhibitor treatment showed an increase or a stabilization of cerebral blood flow in the posterior parieto-temporal and superior frontal regions.

A recent study showed decreased regional cerebral blood flow in the parietal cortex, and an increase in the frontal and the limbic cortices after 18 months of treatment with donepezil or galantamine. ***Case reports and investigations with small sample sizes have reported increased cerebral blood flow after treatment with cholinesterase inhibitors in patients with vascular dementia, dementia with Lewy bodies, and dementia of Parkinson's disease.*** The clinical impact of these haemodynamic events has not been clarified. [12, Rank 4]

> **"Patients with Alzheimer's disease dementia receiving a single dose of cholinesterase inhibitor treatment showed an increase or a stabilization of cerebral blood flow in the posterior parieto-temporal and superior frontal regions"**

Diagnostic Framework in Management of Alzheimer's Disease in Primary Care Settings

With the development of Alzheimer Disease pathologic markers, preclinical Alzheimer Disease are now considered when these markers are present in cognitively normal individuals. However, the challenges to provide a unified definition for cognitive health, for cognitive decline, and for the best signature of in vivo Alzheimer Disease pathology remain to be resolved. The great heterogeneity of methodologies used in different studies referring to different definitions of preclinical Alzheimer Disease has created confusion. Standardizing of these definitions is important to future Alzheimer Disease research.

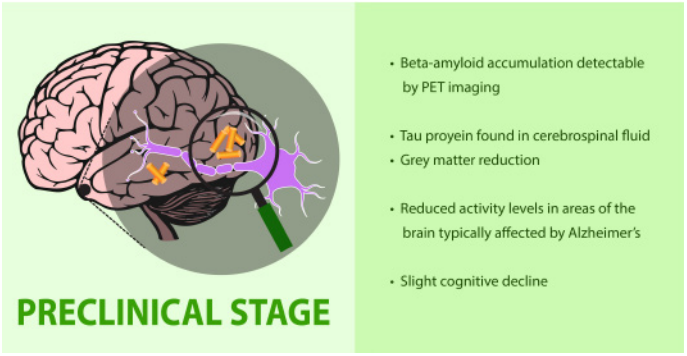

Figure 7: preclinical stage of Alzheimer's disease

In the last decade, a conceptual shift has occurred in the field of Alzheimer Disease with development of a new diagnostic framework. ***A new disease model that begins with risk factor assessment (directed at the potential for primary prevention), advances to screening (for early***

detection and early intervention of disease—secondary prevention), proceeds through diagnosis and staging, and leads to treatments and monitoring of treatment effects has been formulated. This approach includes screening with tests having high sensitivity, lower specificity, and low cost. Individuals enter into the algorithm at different points according to the manner in which they present clinically. Broadly, this can be divided into those who are asymptomatic and those who are symptomatic. Screening asymptomatic individuals provides the basis for preventive approaches. [14, Rank 3]

This new approach of Alzheimer Disease mainly results from interest in revealing patients in the preclinical stage. Individuals can now be identified as being in the preclinical state by the in vivo evidence of Alzheimer pathology (AP), for example, by a biological or molecular "signature" of Alzheimer Disease..

CSF tau changes have been shown to occur ~15 years before the onset of clinical Alzheimer Disease. Similarly, a decline in CSF Ab42 is predicted in analysis up to 20 years before symptom onset. This construct has also been validated in those asymptomatic at risk for clinical Alzheimer Disease (AR-Alzheimer Disease), where altered CSF levels of Alzheimer pathology biomarkers can precede the occurrence of the dementia stage by several years.

Based on both in vivo and postmortem evidence, a hypothetical model outlining potential dynamic changes of Alzheimer Disease biomarker classes have been postulated. According to this model, lowering of CSF brain amyloid tracer uptake is expected before the presence of biomarkers of neuronal injury, regional structural brain changes, and ultimately clinical changes such as decline of memory and cognitive functions with a significant impact on activities of daily living. This preclinical Alzheimer Disease stage is important for studies aimed at prevention of progression to the clinical state. This model also helps for research into novel bio-markers that might verify therapies with early disease modification. At current point of time, a better understanding of the natural history

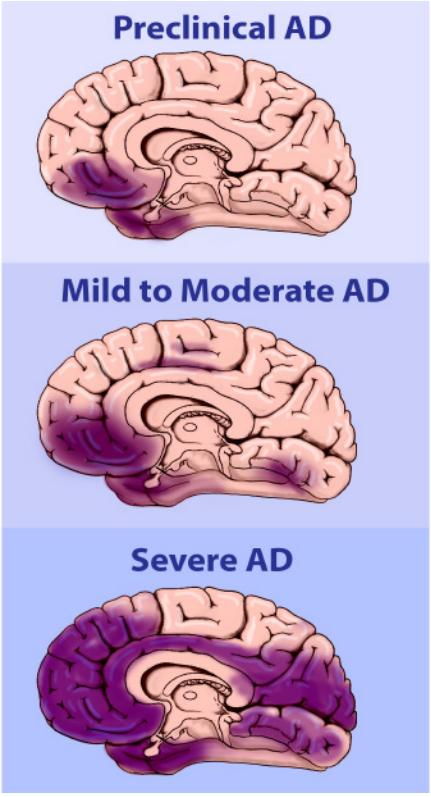

Figure 8: Structural changes of brain in each stage of Alzheimer's disease

of the preclinical stage, the evolution of pathophysiology and structural brain alterations(As shown in fig:8), the influencing factors (i.e., triggers) of disease progression etc. are needed for a concrete picture of the development of Alzheimer Disease.. [13, Rank 5]

" The preclinical Alzheimer Disease stage is important for studies aimed at prevention of progression to the clinical state, as well as for research into novel bio-markers that might verify therapies with early disease modification. A better understanding of the natural history of the preclinical stage, the evolution of pathophysiology and structural brain alterations, the influencing factors (i.e., triggers) of disease progression, and related ethical issues is needed "

Factors Deciding Classification and Stratification of Alzheimer's Disease

Different classifications of preclinical states have been proposed. The international working group (IWG) has defined two different preclinical states: the pre-symptomatic and the asymptomatic at risk state. The entity named pre-symptomatic Alzheimer Disease recognizes the fact that some individuals are virtually destined to develop full clinical Alzheimer Disease, because they are known to carry an autosomal dominant monogenic mutation. The disease, whatever its stage, can be diagnosed with the identification of the mutation. An "asymptomatic at risk" state is more controversial. To be classified as asymptomatic at risk, by definition, individuals must not have clinical evidence of prodromal (the period between initial symptom and complete onset of disease) Alzheimer disease. According to the recent IWG revision, preclinical states of Alzheimer Disease require the absence of clinical signs and symptoms of Alzheimer Disease (both typical or atypical phenotypes) and the presence of at least one biomarker of Alzheimer's pathology. [21, Rank 2]

A staging classification for the asymptomatic at risk state may also be considered aiming at stratifying patients on the basis of biomarkers. The National Institute on Aging/Alzheimer Association (NIA/AA) approach created based on the biomarker model has proposed two hypothetical subgroups. Stage 1 group showing in vivo evidence of amyloidosis in the brain by either PET or CSF biomarkers and stage 2 showing in vivo evidence of both amyloidosis and neurodegeneration. [18, Rank 3].

In addition, the model is largely conceptualized from cross-sectional observations in autosomal dominant Alzheimer Disease (ADAD) subjects. There are circumstances where pathologic tau hyperphosphorylation and the related neurodegeneration process begin ahead of brain amyloidopathy (tau first). [18, Rank 4]

Another staging classification can be

> **" Different classifications of preclinical states have been proposed. The international working group (IWG) has defined two different preclinical states "**

determined based on a low and/or high risk to develop clinical Alzheimer Disease. ***The risk—defined***(As shown in fig:9) as the probability for a patient to develop the clinical symptoms in the rest of his or her lifetime—is due to how fast the patient is progressing by considering presence of established ***risk-enhancing modifiable or non-modifiable factors, such as age, modifying genes, cognitive reserve, comorbidities,*** and so forth and, how advanced the subject and/or patient is on his/her curve of progression (stage of biomarker expression). In this regard, cognitively normal elderly individuals are at very high risk to develop clinical Alzheimer Disease and present a particularly meaningful target population for research projects on asymptomatic at risk state. Observational studies are needed to better know the influencing factors (factors of prevention and risk factors) that may determine the staging of risk [25, Rank 4]

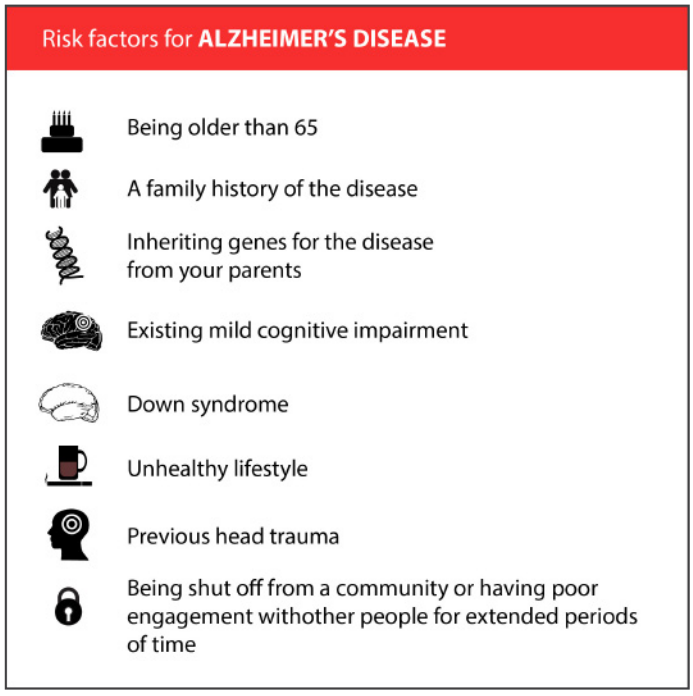

Figure 9: Risk factors of Alzheimer's disease

Identifying the Starting Point of Alzheimer's Disease

It has been proposed that the presence of at least one marker of brain amyloidosis in CSF or PET in cognitively normal individuals may be sufficient to establish the diagnosis of Alzheimer Disease, even in the absence of any clinical manifestations. In line with this consideration, any individual with brain amyloidosis might be treated with disease-modifying drugs in the future although there is no definitive evidence that all these individuals will eventually develop the disease at a later time. An alternative consideration is that amyloidosis is at least necessary and obligatory for an Alzheimer Disease diagnosis, but not sufficient to reliably predict further progression to a symptomatic stage of disease.

Defining disease start is important in light of preventive intervention. Thus, it is important to ascertain what propor-

tion of cognitively healthy individuals, with positive bio-markers, will progress to the clinical state of Alzheimer Disease. There are data indicating that the speed of progression is variable from one subject to the next. Elderly patients with a predominant limbic form of the disease have generally a less-aggressive disease dynamic compared to the neocortical form with hippocampal sparing type that can present in younger patients particularly with focal cognitive signs. The concept of "cognitive reserve" has been proposed to describe the apparently good tolerance (or perhaps resistance) of developing neuropathologic lesions in some individuals. [22, Rank 3]

Notwithstanding the heterogeneity of sporadic Alzheimer Disease, physiological age-related alterations have to be separated from pathologic changes occurring in the brain(As shown in fig:10) that are caused by the underlying Alzheimer Disease process. This is complicated by the fact that there is likely a dynamic and overlapping continuum between Alzheimer Disease and aging. [26, Rank 4]

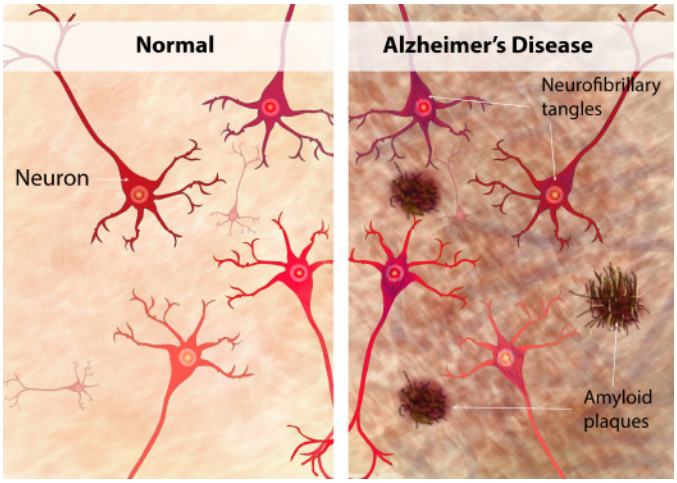

Figure 10: Pathological changes of brain tissue occur in Alzheimer's disease

Amyloid deposition in the brain(As shown in fig:11) seems to have a closer link to Alzheimer Disease-related pathophysiology and may be a better disease marker though it too has an increasing prevalence with age. Its age-related increase advances to a point where it is nearly always described to some extent in healthy normal individuals on postmortem analysis. [28, Rank 5]

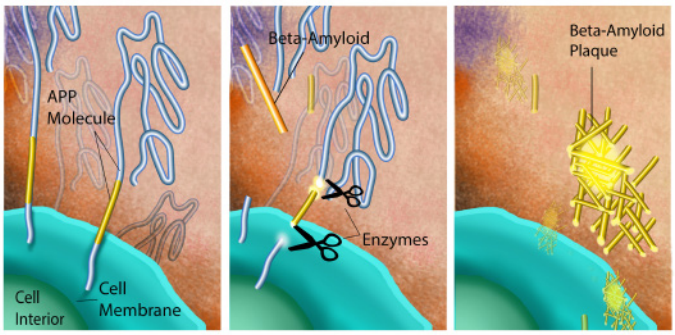

Figure 11: formation and deposition of Amyloid plaque in the brain

Neuropathologic Features Involved In Diagnosis of Alzheimer's Disease in Primary Care Settings

Alzheimer Disease in general has a multifaceted pathophysiology displaying a highly complex genetic heterogeneity. Different mutations in the same gene can result in clinically distinct syndromes

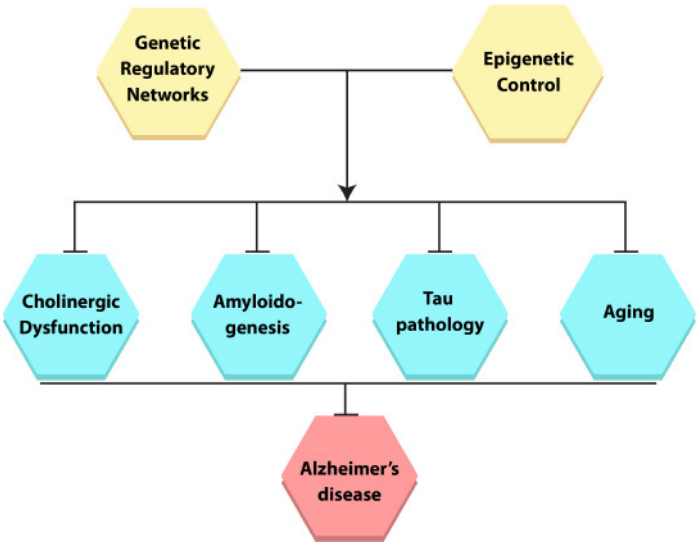

Figure 12: Genetic influence on Alzheimer's disease

(phenotypes). For these reasons, Alzheimer Disease is defined as a "genetically complex" disease.

Alzheimer Disease can be expressed with both the existence of (1) dominantly inherited and (2) nondominantly inherited forms of the disease(As shown in fig:12). The former, owing to a mutation in amyloid precursor protein, is referred to as familial Alzheimer Disease (FAD). FAD accounts for <1% of all Alzheimer Disease cases and presents as classic Mendelian ADAD, often with early (<65 years) age of onset. The latter, commonly defined as sporadic Alzheimer Disease (SAD) as it does not always display obvious familial aggregation, accounts for >99% of all Alzheimer Disease cases. These individuals develop late-onset Alzheimer Disease (LOAD), which usually presents after 65 years(Example As shown in fig:13 and fig:14) . The rare form of dominantly inherited FAD has been traditionally considered as a model of Alzheimer Disease mechanisms that may underlie the much more common SAD. [27, Rank 2]

Pre-symptomatic mutation carrier individuals may provide important clues on biomarkers associated with the preclinical state of the disease. They are also of potential utility to investigate the efficacy of disease-modifying agents in delaying the clinical onset of the disease. It remains uncertain whether it is possible to transpose data derived from familial Alzheimer Disease on the whole spectrum of sporadic Alzheimer Disease. Familial cases of the disease appear to have the same clinical and pathologic phenotypes as sporadic cases. Notably, a study designed to investigate the existence of specific differences in the clinical features of FAD and SAD revealed that—apart from the age of onset, where a positive family history of dementia was associated with an earlier beginning—no major differences including rate of cogni-

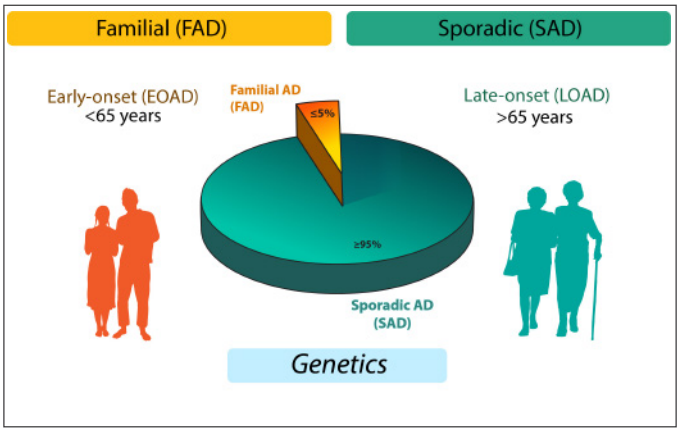

Figure 13: Graphical representation of relation between age and Alzheimer's disease subtypes

tive decline, duration of illness, and presence of non-cognitive symptoms - were reported between FAD patients compared to patients with sporadic disease.

In another study, Alzheimer Disease patients were examined to test the hypothesis that cases with a familial aggregation differ from cases without such an aggregation with reference to cognitive impairment. After evaluating cognitive function, the results did not yield statistically significant differences between the two groups for any of the neurocognitive domains analyzed. Therefore, the hypothesis that the presence of a familial aggregation might result in a distinct phenotype in Alzheimer Disease was not confirmed. The neuropathology of FAD also appears to be similar to that of sporadic cases. In another study, the density of neurofibrillary tangles and senile plaques was compared in different cortical areas, the amygdala, the hippocampus, the parahippocampal gyrus, and the cerebellum in FAD patients and SAD patients with early, intermediate, and late ages of onset of dementia and in age-matched controls. In all brain regions, cases showed more severe alterations than controls. Of note, no substantial differences were observed in the severity scores of neurofibrillary tangles and senile plaques between FAD and SAD. An inverse correlation between age of onset of dementia and the density of neurofibrillary tangles and senile plaques was reported in all regions in FAD and SAD combined. However, the pathophysiological mechanisms underlying amyloid accumulation may differ. In summary, no compelling indication that the neuropathologic features of FAD differ from those of SAD was found. [29, Rank 2]

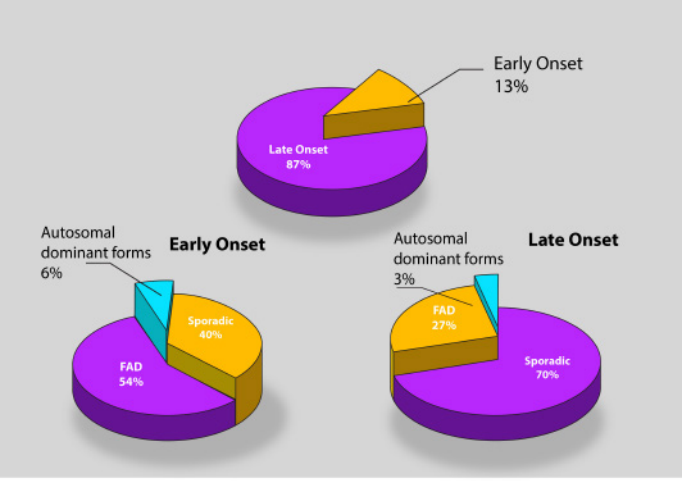

Figure 14 : Graphical representation of onset and Alzheimer's disease subtype

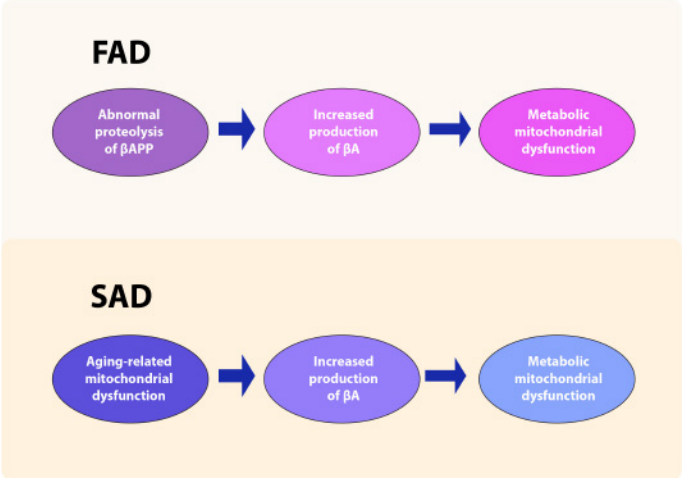

Figure 15: Comparison between Alzheimer's disease subtypes

The Biomarkers Required for Identifying Alzheimer's Disease

Several biomarkers(As shown in fig:16) are currently proposed as indicators of the "asymptomatic at risk" state candidates. These bio-markers have recently divided(As shown in fig:17) into (1) pathophysiological/diagnostic markers, reflecting Alzheimer Disease pathology at any point on the disease continuum and (2) topographical and/or prognostic markers, reflecting "downstream" damage.

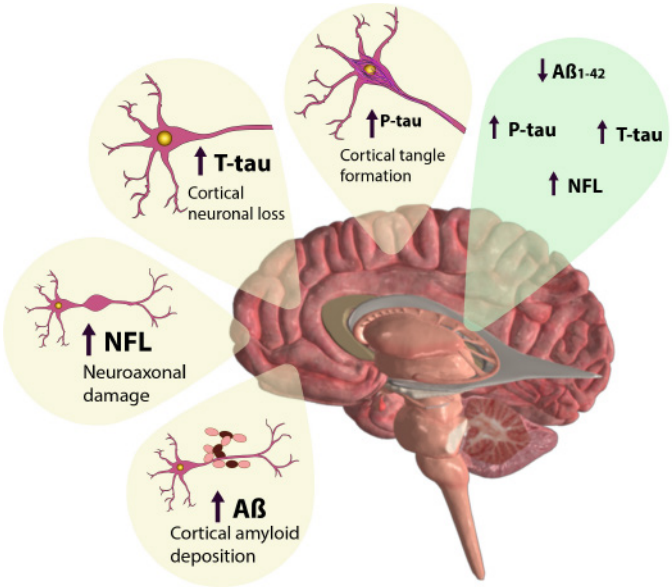

Figure 16: Biomarkers in Alzheimer's disease

The pathophysiological markers of Alzheimer Disease are those indicating the specific presence of tau pathology (CSF or PET tau) and amyloid pathology (CSF Aβ 42 or PET amyloid), whereas the topographical markers include volume changes in the brain (hippocampal atrophy, cortical thickness, and others) assessed by MRI and

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes ✓	No ✗
Total tau, phospho-tau	Yes ✓	No ✗
PET		
Amyloid tracer uptake	Yes ✓	No ✗
Fluorodeoxyglucose	No ✗	Yes ✓
Structural MRI		
Medial temporal atrophy	No ✗	Yes ✓

Figure 17: comparison of two types of biomarkers in Alzheimer's disease

hypometabolism of neocortical regions measured by fluorodeoxyglucose (FDG)—PET. The consideration of how these biomarkers can be used to define preclinical Alzheimer Disease requires further consideration. [24, Rank 1]

Topographical Biomarkers

Topographical markers alone are insufficient for identifying the presence of preclinical Alzheimer Disease stage, although functional changes have been reported to occur in the brains of healthy subjects who are biomarker positive. Although such alterations are suggestive of an ongoing pathologic process, there is no way to ascertain that this downstream process corresponds to Alzheimer Disease pathology in asymptomatic at-risk individuals. The same consideration may apply for MRI-related morphologic changes (cortical thinning, enlargement of sulci, hippocampal atrophy), as it has been recognized that these alterations generally occur later in the

continuum of Alzheimer Disease pathology and that they are not specific for Alzheimer Disease. However, the identification of a specific network of atrophy involving different connected areas may turn out to be an accurate and early marker of Alzheimer Disease. This needs to be demonstrated. [20, Rank 3]

Pathophysiological Biomarkers

Alzheimer Disease is conceptually defined by the presence of biomarkers of Alzheimer Disease pathology. It remains to be shown that this holds true for the preclinical stage of Alzheimer Disease. A recent meta-analysis estimated the prevalence of Aβ biomarker positivity (as defined by either CSF Aβ42 or amyloid PET) in nearly 3000 cognitively normal

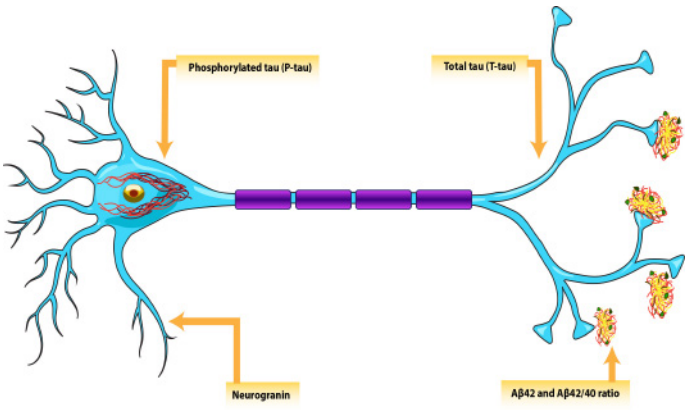

Figure 18: Pathophysiological biomarkers

individuals. The prevalence of amyloid positivity was estimated at 10.4% at age 50 years, increasing by 3%–5% every 5 years of life to an estimated 43.8% at age 90 years. Amyloid positivity correlated very strongly with presence of the APOE allele, with carriers 2–3 times more likely to show positive amyloid biomarkers than noncarriers in each age stratification. [17, Rank 2]

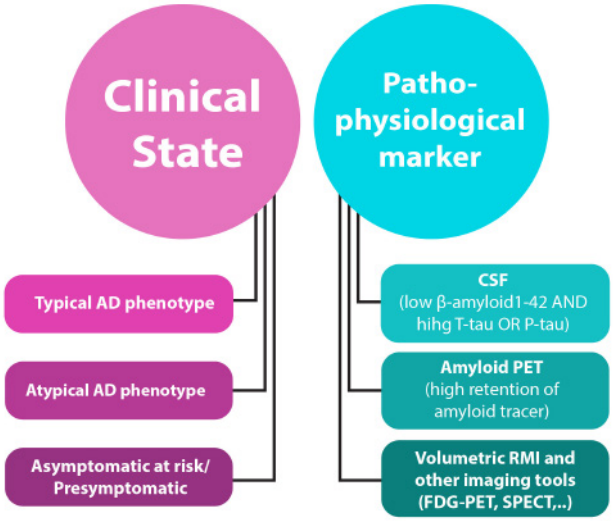

Figure 19: Pathophysiological biomarkers in different clinical state

Management of Alzheimer's Disease by Suggesting Earliest Detection

Longitudinal studies in cognitively healthy individuals showed a correlation between baseline levels of CSF bio-markers and further development of prodromal Alzheimer Disease. Results in preclinical PSEN1 mutation carriers or subjects with subjective memory complaints show that low levels are the best indicator of progression in asymptomatic at-risk patients. Taken together, these data suggest that at the beginning of the preclinical state, amyloid may be the first positive marker. [23, Rank 3]

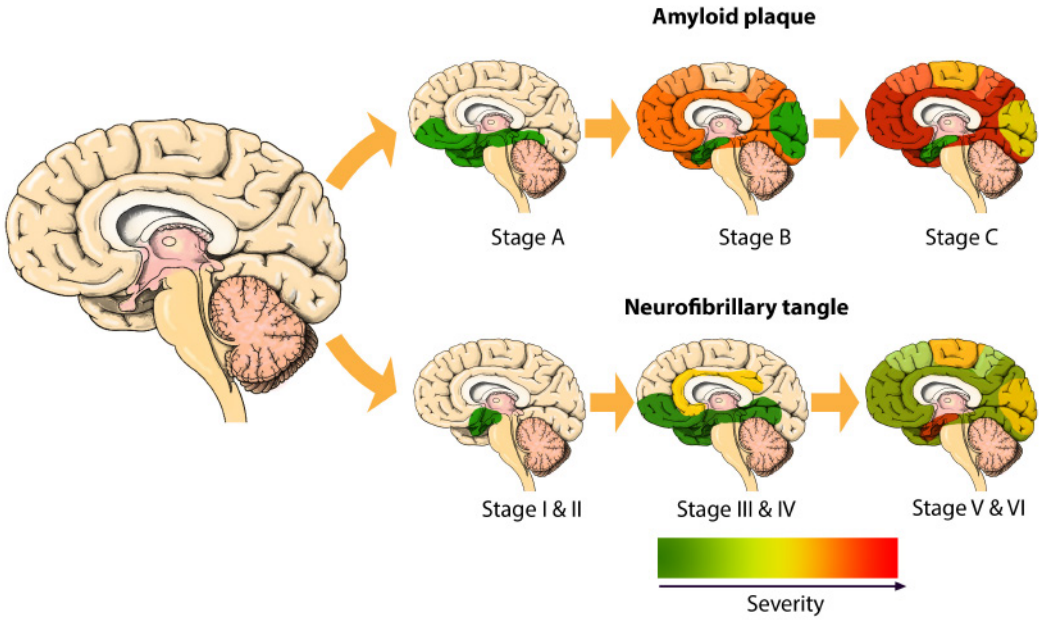

Figure 20: CSF biomarkers in Alzheimer's disease

Other studies showed that in subjects with low-CSF, the additional presence of MRI or CSF tau alterations was indicative of faster progression to a clinical state. Furthermore, a recent large meta-analysis on cross-sectional data showed that Aβ deposition occurs in an age-dependent fashion and also inferred a 20- to 30-year interval between first development of amyloid positivity and onset of dementia. This would put CSF alone in the category for best "state" marker for AR-Alzheimer Disease. In Alzheimer Disease, CSF tau changes may not only be considered as nonspecific (downstream) markers of neuronal death, as seen in other neurodegenerative diseases, but also as a more-specific pathophysiological marker of Alzheimer Disease in relation to neurofibrillary tangles.

Based on the above considerations, the presence of both CSF biomarkers(As shown in fig:20) (increased levels of tau and low levels of Aβ42) significantly increases the specificity for the diagnosis of an "asymptomatic at risk" state, similar to the use in the clinical phase of the disease. [22, Rank 4]

Standardization of Operating Procedures in Diagnosis of Alzheimer's Disease in Primary Care

In the absence of any clinical changes in asymptomatic subjects, the unique link with the underlying disease in a given individual is the evidence of score in biomarkers above the reference threshold. Therefore, the validity of the measure is essential because of ethical consequences of disclosure of a wrong condition. Implementation of standardized procedures (SOP) is of special importance for preclinical Alzheimer

Disease diagnosis. However, both amyloid PET and CSF biomarker measures are subject to significant methodologic variations, which can substantially affect the different cut-off values.

CSF Standardization

With reference to the CSF biomarkers, differences in pre-analytical protocols, analytical procedures, assays quality together with discrepancies in absolute levels between assay formats introduce variability and warrant assay-specific cut-offs. At present, each laboratory has to establish their own internally validated cut-off values and a rigorous analytical quality system, including certified procedures, methodologies, and bridging of batches, to guarantee longitudinal stability in its measurements. For this reason, international standardization efforts have been initiated: the Alzheimer's Association Global Biomarkers Standardization Consortium and International Federation of Clinical Chemistry Working Group for CSF proteins. The aim was to propose protocols harmonizing laboratory practices, defining procedures on CSF collection and handling, creating certified reference materials for assay calibration, and establishing reference measurement procedures. [18, Rank 4]

Amyloid PET Standardization

The type of amyloid ligand used, thresholds established, methods used for amyloid PET imaging processing(As shown in fig:21), target and reference regions used, partial volume correction, acquisition time duration, and potential head movements represent possible confounding factors and introduce variability, thus substantially affecting the cut-off points used. Given the pressing importance of the need for standardization, a working group has been set up to standardize quantitative amyloid imaging measures by scaling the outcome of each particular tracer or analysis method to a 0-to-100 scale, anchored by young controls (≤45 years), and typical Alzheimer Disease patients. [16, Rank 2]

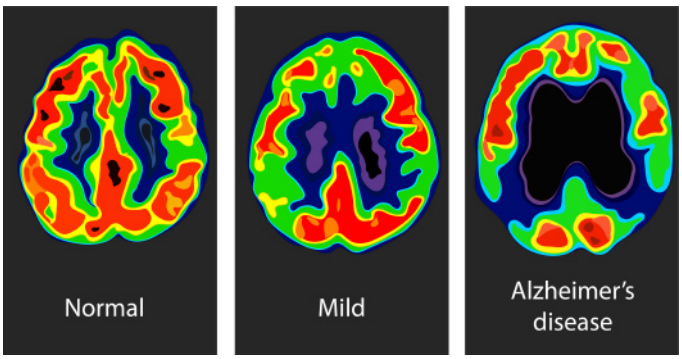

Figure 21: Amyloid PET image

Influence of Additional Mediators in Alzheimer's Disease

The identification of AR-Alzheimer Disease subjects should rely only on the presence of a pathophysiological biomarker. These changes implicate the existence of Alzheimer Disease pathology, which is necessary for further developing the clinical disease. Even with high levels of ligand retention as typically seen in subjects with Alzheimer Disease, some elderly individuals show little if any cognitive disturbances, therefore suggesting the influence of additional mediators such as cognitive reserve.

On the other hand, the process can be accelerated by several factors affecting the risk and/or the rate of progression. It can be speculated that the occurrence of clinical onset of Alzheimer Disease is the expression of a complex algorithm where the presence of Alzheimer Disease brain lesions plays a key role and additional positive and/or negative factors need to be considered. [25, Rank 5]

Risk factors of Alzheimer's Disease

Alzheimer Disease is increasingly recognized as a complex multifactorial disease given the interconnection of the genetic component with ***other risk factors*** such as co-morbidity, vascular risk factors, environmental, and lifestyle factors. A recent meta-analysis on lifestyle modifiable risk factors made use of a mixed-method approach combining findings from a systematic literature review and a consensus study. The study revealed several somatic and lifestyle factors for Alzheimer Disease including depression, (midlife) hypertension, (midlife) obesity, diabetes, physical inactivity, smoking, and low education. It has been estimated that about one-third of Alzheimer Disease dementia cases worldwide might be attributable to the above-mentioned modifiable risk factors. This estimate accounts for the frequent co-occurrence of these risk factors in the same individual. Two main aspects need to be considered when weighting the role of these risk factors in relation to clinical expression of Alzheimer Disease. One is time at exposure because effect of specific risk/protective factors largely depends on age at which they intervene. Risk factors are unlikely to occur isolated but might interact in a synergistic or antagonistic way or form clusters (e.g. metabolic syndrome). For most of these risk factors, the mediating pathways are not completely known, for example, whether they are acting on the amyloid process, on the reserve capacities, or on the inflammatory pathway. [30, Rank 4]

Diagnosis of the Transition Phase of Alzheimer's Disease

After identifying subjects at risk for Alzheimer Disease based on the presence of specific biological predictors, the main issue is to detect those with the highest likelihood to progress to definite clinical Alzheimer Disease in the forthcoming months to years. Full-blown Alzheimer Disease may arise several years (>15 years) after the initial detection of a positive biomarker. Consequently, the long-term treatment of cognitively normal individuals with medications having potentially significant and serious side effects (e.g., amyloid related imaging abnormalities]) remains an uncertain value proposition. Owing to ethical, financial, and medical constraints, it may be important to identify and treat only subjects having the highest risk of developing clinical Alzheimer Disease within a short time frame. For that reason, the identification of markers, able to detect disease progression in a relative short time frame before the onset of clinical symptoms, becomes of crucial importance. [28, Rank 3]

The impact of Alzheimer Disease on objective measures of cognition and clinical manifestations is a gradual process beginning in the preclinical phase and continuing progressively but inexorably into the prodromal and dementia stages, making it impossible to define a discrete onset of the clinical state. The preclinical stage progresses unnoticeably and clinical manifestations are eventually apparent but without a discrete onset. Growing evidence of neuropathologic progression as well as subtle cognitive decline among asymptomatic individuals with brain amyloid supports this view. [34, Rank 2]

Innervation of Neuropathology of Alzheimer's Disease

The cholinergic loss is one of the most prominent components of the neuropathology of Alzheimer's disease. Researchers autopsied the brains of people with Alzheimer's disease and reported a selective and statistically significant reduction in the activity of choline acetyltransferase in the limbic system and cerebral cortex. At the time, the origin of this cholinergic innervation was unknown. In axonal transport studies, combined with cholinergic histochemistry, revealed the Nucleus Basalis of Meynert as the source of cholinergic innervation in the cerebral cortex of the primate brain. These studies led to the investigation of the Nucleus Basalis of Meynert in Alzheimer's disease. The post-mortem data demonstrated a profound loss of cholinergic neurons in the basal forebrain, specifically the Nucleus Basalis of Meynert , of patients with Alzheimer's disease. The Nucleus Basalis of Meynert innervates the entire cerebral cortex and limbic system,

including the hippocampus, and the entorhinal cortex.

It has been well established that cholinergic deficits play a key role in the neuropathology of Alzheimer's disease, not only in late disease, but in preclinical and early stages as well. Accumulated abnormal phosphorylated tau, in the form of neurofibrillary tangles and pretangles, has been found specifically in the cholinergic neurons of the basal forebrain in cognitively normal elderly subjects. A progression of abnormalities has been observed in the cholinergic neurons of the basal forebrain of non-demented younger adults, non-demented elderly people, and people with mild or severe Alzheimer's disease. [33, Rank 5]

Thickened cholinergic nerve fibres and ballooned terminals, demonstrated in middle-aged adults, have been shown to increase with age, suggesting that cholinergic loss in established Alzheimer's disease is preceded by this cholinergic pathology. Cholinergic function outside of the Nucleus Basalis of Meynert - namely, in the caudate, putamen, and thalamus - appears relatively spared in this process. There is, therefore, no generalized 'cholinergic vulnerability' in Alzheimer's disease but, instead, a preferential vulnerability of the Nucleus Basalis of Meynert . The underlying mechanism may be the location of the Nucleus Basalis of Meynert within the corticoid-limbic belt of the forebrain, which includes other limbic structures such as the hippocampus, amygdala, and entorhinal cortex. These are the, areas that are collectively the most vulnerable to neurofibrillary degeneration and neurofibrillary tangle formation in the ageing–Alzheimer's disease continuum.

With the use of longitudinal MRIs and amyloid-β biomarkers, it has been shown that volume loss in the Nucleus Basalis of Meynert precedes and predicts memory impairment and degeneration of the entorhinal cortex. This observed relationship strengthens the conclusion that the loss of Nucleus Basalis of Meynert neurons is an early and perhaps also clinically relevant event in Alzheimer's disease.

Unlike the cholinergic neurons and synaptic terminations of the caudate, putamen, and thalamus, the Nucleus Basalis of Meynert and medial septum cholinergic neurons are fully dependent on the retrograde transport of nerve growth factor (Nerve Growth Factor) for the maintenance of their anatomic and biochemical characteristics and their terminal synapses in the cerebral cortex and hippocampus. [32, Rank 2]

It is well accepted that the interactions of Nerve Growth Factor with the forebrain cholinergic system is of significance in Alzheimer's disease. There is evidence that cholinergic neurons in the Nucleus Basalis of Meynert may well be deprived of trophic support even before

clinical manifestations of Alzheimer's disease. While the biosynthesis of Nerve Growth Factor in the cerebral cortex is not affected in Alzheimer's disease, experimental animal data and human post-mortem brain material would indicate that trophic support of the Nerve Growth Factor-dependent cholinergic neurons in the Nucleus Basalis of Meynert may be compromised by defective retrograde transport of Nerve Growth Factor or the diminished conversion of pre-Nerve Growth Factor to mature Nerve Growth Factor (neuroguidin). In individuals with Down syndrome, who are at high risk for early-onset Alzheimer's disease by amyloid-β-mediated mechanisms, rising plasma levels of amyloid-β and inflammatory markers have been associated with biomarker evidence of Nerve Growth Factor dysregulation.

These data suggest that Nerve Growth Factor dysregulation may be precipitated by the accumulation of amyloid-β and amyloid-β-driven inflammation, the end result of which is cholinergic loss in the Nucleus Basalis of Meynert . The potential downstream effects of amyloid-β on cholinergic neurons in the Nucleus Basalis of Meynert , by way of dysregulated Nerve Growth Factor, deserve further exploration. Therefore, the Nerve Growth Factor metabolic pathway remains a potential pharmacological target in the effort to slow the loss of critical cholinergic function in Alzheimer's disease, especially at preclinical stages. However, intracerebrally- and exogenously-applied Nerve Growth Factor has so far shown to be unsuccessful. It is important to keep in mind that exogenous Nerve Growth Factor may reach undesirable ectopic targets producing undesirable effects (pain, anorexia, other). On the other hand, the pharmacological normalization of the Nerve Growth Factor metabolic pathway, if attainable at early Alzheimer's disease pathology stages, could potentially halt the Nucleus Basalis of Meynert degeneration by selectively boosting the trophic influence of Nerve Growth Factor with greater physiological selectivity.

Pathology of the Nucleus Basalis of Meynert is not unique to Alzheimer's disease. Synucleinopathies such as Parkinson's disease and especially Lewy body dementia are also associated with Nucleus Basalis of Meynert degeneration and the resultant cortical cholinergic denervation. In Lewy body dementia this effect may be even more severe than in Alzheimer's disease. In contrast to Alzheimer's disease where the Nucleus Basalis of Meynert degeneration is based on neurofibrillary tangle formation, in Lewy body dementia the degeneration is associated with intracellular Lewy bodies. It is interesting that cholinesterase inhibitors can improve cognition also in Parkinson's disease and Lewy body dementia. [36, Rank 3]

The Role of Symptomatic Treatment of Alzheimer's Disease in Primary Care Management

The prevailing therapeutic strategy in the management of Alzheimer's disease is based on the restoration of cholinergic function through the use of compounds that block the enzymes that break down acetylcholine. Cholinesterase inhibitors are designed to inhibit the breakdown of acetylcholine and sustain its activity at cholinergic synapses. Currently available FDA-approved cholinesterase inhibitors for the treatment of Alzheimer's disease are donepezil, rivastigmine, and galantamine. These drugs have been shown to statistically significantly improve cognition, daily and global function, and some behavioural manifestations of Alzheimer's disease, compared with placebo treatment. As such, cholinesterase inhibitors are generally considered symptomatic treatments for Alzheimer's disease. For the purpose of the discussion on therapy, we will use the term 'Alzheimer's disease' to mean 'Alzheimer disease dementia' rather than 'Alzheimer disease pathology.' This distinction is important because Alzheimer's pathology emerges many years before symptom onset and there are currently no approved guidelines concerning cholinergic therapy during preclinical stages of the disease.

A meta-analysis of studies of donepezil, rivastigmine, and galantamine showed a modest but clinically meaningful overall benefit of these drugs for stabilizing cognition, function, behaviour, and global clinical change. Results from the few existing head-to-head comparisons of cholinesterase inhibitors have been mixed; however, an adjusted analysis of placebo-controlled data suggested that donepezil might have a slight advantage over rivastigmine and galantamine in efficacy and tolerability. These results did not include the rivastigmine transdermal delivery system, which has fewer side effects than the oral formulation of rivastigmine. In a systematic review of seven studies that examined the economics of cholinesterase inhibitors, treatment of Alzheimer's disease with cholinesterase inhibitors appeared to be a cost-effective, if not a cost-saving, strategy—although a considerable number of variables, such as the length of treatment and medication discounts, contributed to general uncertainty as to their benefits. A large Medicare beneficiary study concluded that each additional month of cholinesterase inhibitors treatment is associated with a 1% reduction in total all-cause healthcare costs. [35, Rank 2]

Long-term data indicate that the use of a cholinesterase inhibitor in Alzheimer's disease reduces the risk for nursing home placement by ~30% for each year of treatment. In addition, patients with Alzheimer's disease who are treated with a higher

mean dose of cholinesterase inhibitors compared with patients receiving a lower mean dose have been shown to experience delayed nursing home placement. These data are supported by a post hoc analysis of the trial in which the nursing home placement of community-dwelling patients with moderate-severe Alzheimer's disease was assessed. Patients who were randomized to discontinue donepezil therapy (10 mg/day) were twice as likely to enter a nursing home after 1 year as were individuals who continued treatment with cholinesterase inhibitors; however, this effect lost statistical significance after 3 years. Finally, cholinesterase inhibitors have also been shown to reduce the burden experienced by caregivers of patients with Alzheimer's disease, by reducing caregiver time devoted to the patient, caregiver stress, and some of the behavioural symptoms. [23, Rank 3]

Additional data from both laboratory-based investigations and clinical trials have suggested that cholinesterase inhibitors may have a broader mechanism of action than enhancing cholinergic activity and that these drugs are associated with a stabilizing effect on the course of Alzheimer's disease dementia that may be greater than expected by cholinesterase inhibition alone. Prospective long-term observational studies suggest that cholinesterase inhibitors offer a benefit over the long-term course of Alzheimer's disease. Cognitive decline has been observed to occur significantly more slowly with cholinesterase inhibitors compared with no treatment, suggesting a delay relative to typical clinical course. These observations are supported by other long-term data showing declines in cognitive and global functioning were slower with the persistent use of donepezil over a mean follow-up period of 3 years. At least two other prospective observational Alzheimer's disease studies offer similar results, demonstrating slower cognitive and functional deterioration with the persistent and continued use of cholinesterase inhibitors.

Suboptimal Use of Cholinesterase Inhibitors in Alzheimer's Disease

Despite clinical data and guideline recommendations supporting the use of cholinesterase inhibitors throughout all stages of Alzheimer's disease, these drugs are often inappropriately regarded as ineffective in Alzheimer's disease and therefore are underused. According to a survey of outpatient visits for Alzheimer's disease specifically or dementia more generally, fewer than half (46%) of patients were prescribed cholinesterase inhibitors, with donepezil being the most frequently prescribed. Of note, psychiatrists and neurologists were significantly more likely to prescribe cholinesterase

inhibitors than were other physicians.

In a survey of physicians, doctors reported that they would be more likely to prescribe a cholinesterase inhibitor if it enabled a person with mild Alzheimer's disease to remain clinically stable for 15 months and a person with moderate Alzheimer's disease to remain clinically stable for 11 months. Survey responses also suggested that a cholinesterase inhibitor prescription was more likely if a physician had less stringent requirements for clinical efficacy. In another survey, primary care physicians held mostly ambivalent or negative views about cholinesterase inhibitor treatment for dementia. Potential barriers to the use of cholinesterase inhibitors were physicians' lack of knowledge and experience with cholinesterase inhibitor treatment, although these primary care clinicians often yielded to pressure from family members to prescribe it.

Overall treatment persistence with cholinesterase inhibitors is suboptimal. In a large Medicare beneficiary study of patients with Alzheimer's disease, treatment persistence at 1 year among patients with Alzheimer's disease who initially received cholinesterase inhibitors ranged from small percentage. Among elderly patients with Alzheimer's disease who received cognition-enhancing drugs, rates of non-persistence; although rates of impersistence were lower in the more recent cohort and in patients taking multiple anti-dementia medications. [40, Rank 1]

Despite physician ambivalence about the efficacy of cholinesterase inhibitors in Alzheimer's disease and their inconsistent and limited use, data support the prescription of cholinesterase inhibitors throughout all stages of the disease. In an analysis of four placebo-controlled studies of people with severe Alzheimer's disease, statistically significant cognitive improvement, and in some cases improvement in global functioning, was observed at 24 or 26 weeks with donepezil treatment at a dosage of 10 mg daily. In a pooled analysis of these trials, relative improvement was observed across all levels of cognitive score, including patients with the most severe cognitive impairment.

In an expansive compilation of cholinesterase inhibitor trials in patients with more advanced Alzheimer's disease, including patients in a nursing home setting, less decline in daily and global function was consistently documented with donepezil or rivastigmine treatment, although clinical evidence supporting rivastigmine use was less extensive. Although choline acetyltransferase activi-

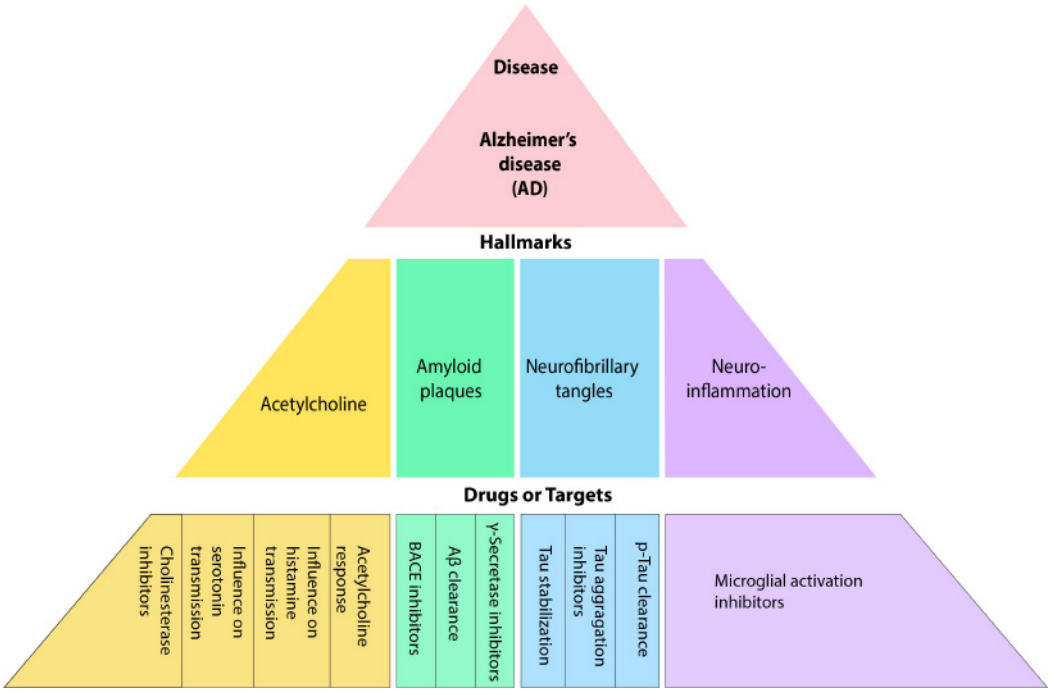

Figure 22: Drug therapy in Alzheimer's disease

ty in the neocortex, as a marker of cholinergic function, keeps declining, some residual choline acetyltransferase activity can be detected in advanced dementia. This suggests that residual cholinergic input may be present in severe Alzheimer's disease and thus provides a biological target for cholinesterase inhibitor therapy in this late stage. Other studies, however, have shown near total destruction of cholinergic axons in the cerebral cortex of patients with advanced Alzheimer's disease, suggesting that the effect of cholinesterase inhibitors at these stages may be mediated through spared cholinergic pathways of the thalamus and basal ganglia rather than cerebral cortex and limbic regions. [19, Rank 5]

Integrating complex disease-related processes: future paradigms and implications

The neuropathological and clinical data summarized above make it very likely that cholinesterase inhibitors or other cholinomimetic interventions will remain essential components of therapy for Alzheimer's disease. The demonstration of early involvement of the cholinergic system starting at preclinical stages of the disease, suggests that cholinomimetics, along with anti-amyloid and anti-tau interventions, may each have a distinct role in disease prevention. Future research and clinical paradigms related to Alzheimer's disease may rely more heavily upon the 'systems biology' approach to the disease, stressing the

interaction of factors such as genetic predisposition, oxidative stress, mitochondrial dysfunction, inflammatory mechanisms, vascular insufficiency, the accumulation of amyloid-β, neurofibrillary degeneration, cholinergic deficits, and other neurotransmitter abnormalities. A systems biology approach explicitly recognizes the multifactorial, dynamic nature of diseases like Alzheimer's disease and helps clinicians customize therapeutic regimens that are targeted at multiple levels of pathology over the course of the disease. [38, Rank 3]

At its most basic level, the pharmacological management of Alzheimer's disease will likely incorporate tailored combination therapies—by using, for example, currently available and novel cognition-enhancing treatments [e.g. cholinesterase inhibitors, NMDA (N-methyl-D-aspartate) receptor antagonists, and other therapies in development] with medications that are potentially disease-modifying (e.g. anti-amyloid-β or anti-tau therapies). As our understanding of Alzheimer's disease pathophysiology expands and we identify additional clinically useful risk factors and biomarkers, the therapeutic approach to Alzheimer's disease will likely parallel the way in which physicians currently manage other complex, variable, and highly idiosyncratic diseases. [37, Rank 3]

An extension of tailored therapy for complex diseases lies at the core of precision medicine, which should guide future strategies for preventing or treating Alzheimer's disease. The ultimate goal of precision medicine is to be able to administer a personalized therapy that specifically targets an individual's known disease risks and disease process at the molecular level. Given the complexity and heterogeneity of Alzheimer's disease pathophysiology, precision medicine may involve the determination of genetic risk profiles, the use of brain imaging, and the detection of biomarkers in plasma or CSF to fashion a specific preventive or therapeutic regimen for a particular individual at risk for or with Alzheimer's disease.

To this end, ongoing trials, such as Dominantly Inherited Alzheimer Network trial, the Alzheimer's Prevention Initiative, and the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease trial, are studying people at high risk for Alzheimer's disease and tracking biomarkers to identify individuals who might be most responsive to specific, targeted, disease-modifying interventions. In the meantime, extensive clinical investigations into cholinesterase inhibi-

tors have already been conducted in broad and largely heterogeneous populations, with success seen across multiple patient 'types' defined by severity and other important characteristics. These developments consolidate the role of cholinomimetic agents as essential elements of the combined pharmacologic treatments for Alzheimer's disease that will be developed in the future. [10, Rank 4]

The cholinergic system is important for neuronal function in memory, learning, and other essential aspects of cognition and plays a wider role in the promotion of neuronal plasticity. Multidisciplinary investigations are revealing how dysfunction in cholinergic networks arising from the basal forebrain, interact with other important pathophysiologic aspects of Alzheimer's disease—including amyloid-β plaques, neurofibrillary tangles, inflammation, oxidative stress, and vascular insufficiency to undermine cognition. A wealth of clinical literature supports the benefit of promoting cholinergic activity in Alzheimer's disease through the use of cholinesterase inhibitors. Moreover, new data based on MRI are showing evidence of hippocampal protection and, perhaps, disease course alterations in individuals who receive cholinesterase inhibitors for long periods of time. Interest remains high in understanding the temporal sequence and cascade of these complex interactions and their synergistic feedback mechanisms over the course of Alzheimer's disease. It is anticipated that optimal Alzheimer's disease management will integrate a systems biology approach based on precision medicine to help tailor combinatorial therapeutic regimens for different stages of Alzheimer's disease on the basis of genetic risks, brain imaging, and biomarkers. As we anticipate major developments in the treatment strategies of Alzheimer's disease, cholinergic interventions are likely to maintain their critical roles in the therapeutic armamentarium. [39, Rank 5]

Conclusion

Preventive factors should be critically considered as they may slow down or postpone the progression to a clinical Alzheimer Disease. The major interest for identifying vascular and lifestyle modifiable risk factors is the possibility of impacting the onset of a clinical Alzheimer Disease by advising and intervening subjects at risk. The multifactorial nature of Alzheimer Disease suggests that multicomponent interventions targeting several risk factors simultaneously might be needed for optimal preventive effects. In the last three decades, several studies, most observational, have underlined the role of modifiable factors in delaying the clinical onset of Alzheimer Disease.

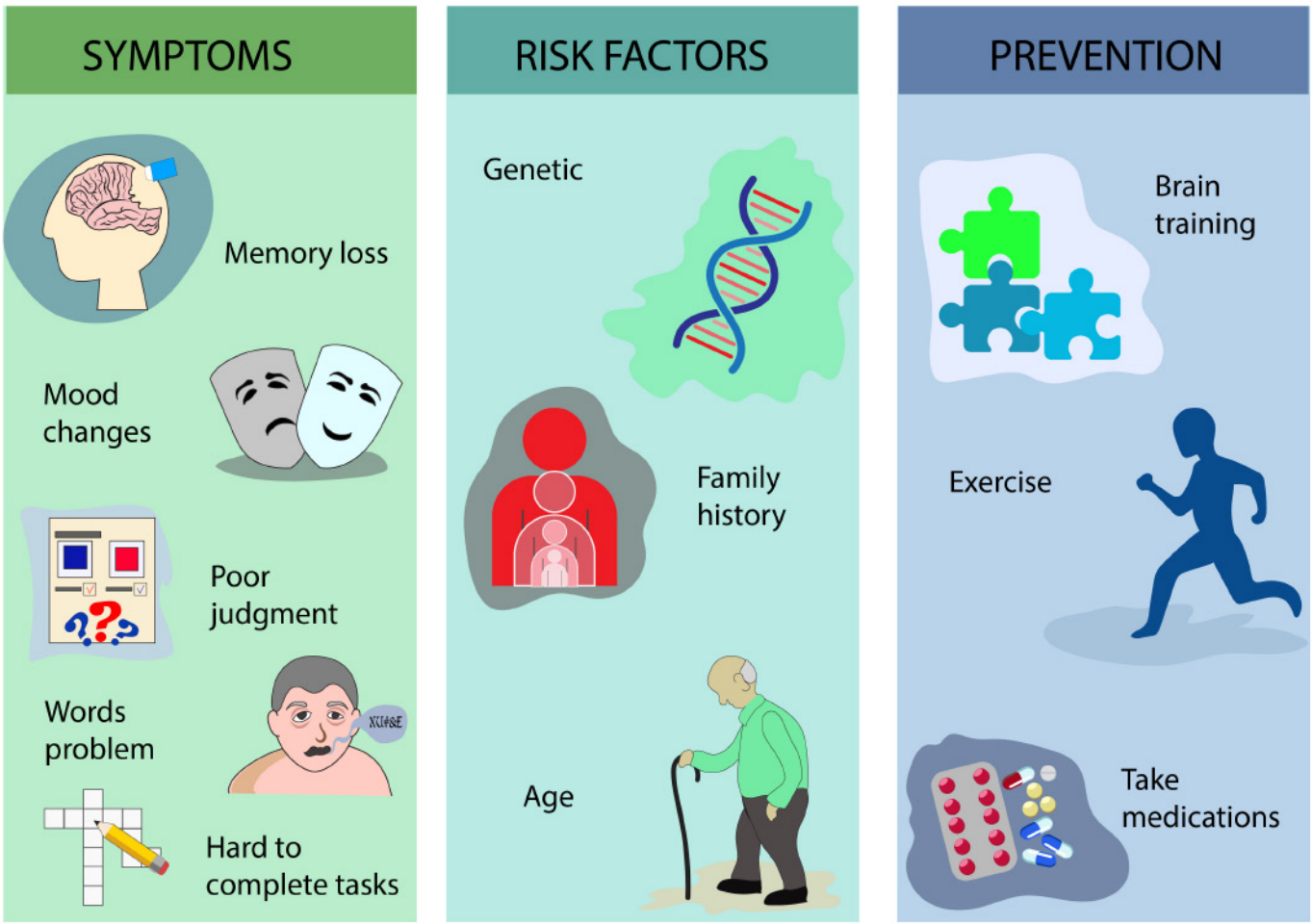

Figure 23: Alzheimer's disease; Symptoms, Risk factors, Prevention

***Important information for post-test are highlighted in red letters, boxes and diagrams.**

References

1. Hubbard BM, Fenton GW, Anderson JM. A quantitative histological study of early clinical and preclinical Alzheimer's disease. Neuropathol Appl Neurobiol 2015
2. Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J, et al. Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. Nat Rev Drug Discov 2015
3. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2016
4. Fagan AM, Xiong C, Jasielec MS, Bateman RJ, Goate AM, Benzinger TL, et al. Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease. Sci Transl Med 2014
5. Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O. Cerebrospinal fluid levels of beta-amyloid 1–42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Arch Gen Psychiatry 2014
6. Delaere O, Mennen U, Van Heerden W, Raubenheimer E, Wiese AM, Boomker D. Side-effects of rinsing fluids on the rat femoral artery. A histological and electron microscopic study. J Hand Surg Br 2017
7. Jack CR Jr, Vemuri P, Wiste HJ, Weigand SD, Aisen PS, Trojanowski JQ, et al. Evidence for ordering of Alzheimer disease biomarkers. Arch Neurol 2018
8. Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2015
9. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2016
10. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guide lines for Alzheimer's disease. Alzheimers Dement 2017
11. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2015

12. Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. Neuron 2015
13. Jack CR Jr, Wiste HJ, Weigand SD, Knopman DS, Lowe V, Vemuri P, et al. Amyloid-first and neurodegeneration-first profiles characterize incident amyloid PET positivity. Neurology 2018
14. Brettschneider J, Del Tredici K, Lee VM, Trojanowski JQ. Spreading of pathology in neurodegenerative diseases: a focus on human studies. Nat Rev Neurosci 2015
15. Heilbronner G, Eisele YS, Langer F, Kaeser SA, Novotny R, Nagarathinam A, et al. Seeded strain-like transmission of beta-amyloid morphotypes in APP transgenic mice. EMBO Rep 2014
16. Nelson PT, Head E, Schmitt FA, Davis PR, Neltner JH, Jicha GA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. Acta Neuropathol 2017
17. Bertram L, Tanzi RE. The genetics of Alzheimer's disease. Prog Mol Biol Transl Sci 2018
18. Jones L, Holmans PA, Hamshere ML, Harold D, Moskvina V, Ivanov D, et al. Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. PLoS One 2016
19. International Genomics of Alzheimer's Disease Consortium. Convergent genetic and expression data implicate immunity in Alzheimer's disease. Alzheimers Dement 2016
20. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. Lancet Neurol 2014
21. Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, et al. Preclinical Alzheimer's disease and its outcome: A longitudinal cohort study. Lancet Neurol 2016
22. Johnson KA, Schultz A, Betensky RA, Becker JA, Sepulcre J, Rentz D, et al. Tau PET imaging in aging and early Alzheimer's disease. Ann Neurol 2016
23. Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2016
24. Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic bio-markers. Lancet Neurol 2015
25. Delaere P, He Y, Fayet G, Duyckaerts C, Hauw JJ. Beta A4 deposits are constant in the brain of the oldest old: An immunocytochemical study of 20 French centenarians. Neurobiol Aging 2015

26. Cavedo E, Pievani M, Boccardi M, Galluzzi S, Bocchetta M, Bonetti M, et al. Medial temporal atrophy in early and late-onset Alzheimer's disease. Neurobiol Aging 2015
27. Braak H, Del Tredici K. The pathological process underlying Alzheimer's disease in individuals under thirty. Acta Neuropathol 2018
28. Duyckaerts C Tau pathology in children and young adults: can you still be unconditionally baptist? Acta Neuropathol 2017
29. Mukaetova-Ladinska EB, Harrington CR, Roth M, Wischik CM. Alterations in tau protein metabolism during normal aging. Dementia 2016
30. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al. Primary age-related tauopathy (PART): A common pathology associated with human aging. Acta Neuropathol 2015
31. Duyckaerts C, Braak H, Brion JP, Buee L, Del Tredici K, Goedert M, et al. PART is part of Alzheimer disease. Acta Neuropathol 2015
32. Villemagne VL, Pike KE, Chetelat G, Ellis KA, Mulligan RS, Bourgeat P, et al. Longi tudinal assessment of Abeta and cognition in aging and Alzheimer disease. Ann Neurol 2016
33. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 2018
34. Khachaturian ZS. Diagnosis of Alzheimer's disease. Arch Neurol 2017
35. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 2016
36. Bertram L, Lill CM, Tanzi RE. The genetics of Alzheimer disease: back to the future. Neuron 2016
37. Holmes C, Lovestone S. The clinical phenotype of familial and sporadic late onset Alzheimer's disease. Int J Geriatr Psychiatry 2018
38. Ryman DC, Acosta-Baena N, Aisen PS, Bird T, Danek A, Fox NC, et al. Symptom onset in autosomal dominant Alzheimer disease: A systematic review and meta-analysis. Neurology 2018
39. Haupt M, Kurz A, Pollmann S, Romero B. Alzheimer's disease: Identical phenotype of familial and non-familial cases. J Neurol 2015
40. Bohnen NI, Djang DS, Herholz K, Anzai Y, Minoshima S. Effectiveness and safety of 18F-FDG PET in the evaluation of dementia: a review of the recent literature. J Nucl Med 2018