New Treatment Investigations for Alzheimer's Disease
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According to the 2012 World Health Organization and Alzheimer's Disease International report, over 35 million people worldwide have dementia with new cases occurring every four seconds. This is equivalent to 7.7 million new cases per year. Based on data from the Alzheimer's Association, approximately 5.2 million people living in the United States in 2013 have Alzheimer's disease (AD). There is an associated increase in AD prevalence and incidence between 65 and 95 years of age (see Table 1). Research has also indicated that there may be a genetic predisposition to Alzheimer's disease with a positive family history being implicated as a risk factor for development. First-degree relative with Alzheimer's disease have a higher lifetime risk of developing the disease than the general population or relatives of individuals who are not demented. Other proposed risk factors include gender (greatest risk for women > 75 years), head trauma, hypothyroidism, vascular disease, hypertension, elevated low density lipoprotein cholesterol, and history of depression.

Table 1. Incidence and Prevalence of Alzheimer's disease in the United States

<table>
<thead>
<tr>
<th>Age range</th>
<th>Prevalence+</th>
<th>Incidence*</th>
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<tbody>
<tr>
<td>&lt; 65 years of age</td>
<td>~4%</td>
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</tr>
<tr>
<td>65-74 years of age</td>
<td>6%</td>
<td>53 new cases/1000 people</td>
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<tr>
<td>75-84 years of age</td>
<td>44%</td>
<td>170 new cases/1000 people</td>
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<tr>
<td>&gt; 85 years of age</td>
<td>46%</td>
<td>231 new cases/1000 people</td>
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</tbody>
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+number of existing cases of a disease in a population at a given time  
* number of new cases of a disease over a time period

Alzheimer's disease is one of the most commonly identified forms of dementia and is defined as a progressive and ultimately fatal neurodegenerative condition which results in loss of neurons in the cortex and other grey matter regions of the brain. Two pathologic processes are involved in
Alzheimer's disease: amyloid plaque accumulation in the brain to decrease cellular transmission, and neurofibrillary tangle involvement, which disrupts neuronal structure and function. The vulnerable brain regions include the amygdala as well as the hippocampus and areas around the hippocampus. The two pathologic changes work to cause chaos within the nervous system to slow transmission and impair the formation of new memories. In addition to the structural changes that occur, there are also changes in neurotransmitters, especially acetylcholine, an important neurotransmitter involved in the formation of memory. Acetylcholine concentrations are reduced either as a result of cellular loss or due to loss of cholinergic neurons in the basal forebrain.

Since the early 1990s, the use of cognitive enhancers (e.g., cholinesterase inhibitors) has become the standard course of management for Alzheimer's disease. Cholinesterase inhibitors inhibit centrally-active acetylcholinesterase, the enzyme responsible for acetylcholine hydrolysis, which leads to increased acetylcholine available for synaptic transmission in the central nervous system. The approval of memantine (Namenda®) in 2003 offered an additional treatment alternative for managing moderate to severe Alzheimer's disease; memantine binds to N-methyl-D-aspartate (NMDA) receptors and blocks the excitotoxic actions of glutamate, a key excitatory neurotransmitter in the brain that plays a role in memory, learning and information processing. Glutamate dysfunction has been implicated in Alzheimer's disease and memantine serves to regulate cerebral glutamate activity.

Although five medications are currently FDA-approved to treat Alzheimer's disease symptoms, none of these drugs treat the underlying cause of the disease. The development of effective disease modifying treatments are urgently needed for optimal disease management. Drug discovery has been largely directed toward the development of disease-modifying medications that counteract the progression of Alzheimer's disease. Over the last thirty years, researchers have strived to make progress in understanding the difference between the functioning healthy brain compared to one that contracts Alzheimer's disease. There have been some promising targets for next-generation drugs therapies that are under investigation in current research studies. Beta-amyloid is recognized as the chief component of plaque and scientists now have a better understanding of how this protein fragment is removed from its parent compound amyloid precursor. Researchers are developing medications that are targeting every point of amyloid processing. This includes preventing the beta-amyloid fragments from clumping into plaques or using antibodies against beta-amyloid as a means of inducing clearance from the brain. Also, tau is the primary component of tangles and the hallmark for brain abnormality. Researchers are investigating methods to keep tau molecules from collapsing and twisting into tangles. Some of the disease-modifying drugs that have been developed to date to include drugs that reduce beta amyloid (Ab) production, drugs that prevent Ab aggregation, drugs that promote Ab clearance, as well as drugs that target tau phosphorylation and assembly.

A new approach to screening for potential new Alzheimer's disease treatments uses Caenorhabditis elegan, a small transplant worm that focuses on tau to help maintain the structure of the brain. This process involves recreating tauopathies and screening approved drug compounds for the purpose of identifying new drug targets. The worm model has identified six compounds that can alleviate tau-induced behavior abnormalities. The human cultured model has demonstrated that azaperone, an antipsychotic drug, has the potential to decrease the amount of identifiable abnormal tau. It has been proposed that other antipsychotic medications may have effects comparable to azaperone, so researchers are performing tests with these compounds in existing mouse models of Alzheimer's disease.

The presence of inflammation is another key abnormality that can be identified in the Alzheimer's brain. Neuro-inflammation is an important factor that has been seen with the progression of Alzheimer's disease. The development of MDA7, a compound with anti-inflammatory properties that acts on the cannabinoid (CB2) receptor, may help to restore memory and cognition, which has been demonstrated in animal models.

The future of Alzheimer's disease research, drug development and subsequent treatments are largely focused on disease identification before symptoms appear or modifying the disease with its onset. In addition to investigating experimental drugs, many clinical trials are moving toward the use of brain imaging studies, blood tests, or biomarkers that will help identify the disease during its earliest and most treatable stages before treatment becomes more complex. While there is currently no cure for Alzheimer's disease, researchers are working diligently to understand the disease progression and formulate new drug treatments based off this improved understanding.
References


