

HEALTH & SCIENCE

Alzheimer's drug trials surge, suggesting new pathways for care

An unprecedented number of drugs are in phase II and phase III studies, but the lack of a definitive diagnostic test hampers efforts.

By [Victoria Stagg Elliott](#), *AMNews* staff. Aug. 18, 2008.

Chicago -- Physicians treating people with Alzheimer's disease are more confident than ever that novel, disease-modifying drugs are on the horizon.

Dozens of compounds that may delay disease onset, slow its progress or ameliorate symptoms are producing promising results in clinical trials. And such findings have triggered optimism -- voiced at the Alzheimer's Assn. International Conference on Alzheimer's Disease, July 26-31.

"The big overarching message is how robust the pipeline is, and how we're developing on all fronts and moving in some unexpected directions," said Sam Gandy, MD, PhD, chair of the Alzheimer's Assn.'s medical and scientific advisory council.

But another side to this story offers a reality check. Along with these positive signs is a sense of urgency, because as baby boomers age, the number of people with Alzheimer's is expected to swell. And therapies now available relieve symptoms for only a few years and do not change the illness's underlying course.

Researchers, therefore, are attacking this disease with pharmaceuticals aimed at an array of targets.

A 12-week trial suggested that PBT2 -- a metal, protein-attenuating compound being developed by Prana Biotechnology Limited -- reduced a toxic form of beta-amyloid in the brain.

Another 12-week investigation found that Allon Therapeutics' AL-108, a nasal spray composed of an eight amino acid peptide that reduces neurofibrillary tangles, led to improvements in those with mild cognitive impairment.

Some of the drugs are not new; rather, they are being examined for potential novel uses. An 18-month investigation of Dimebon (dimebolin hydrochloride), a decades-old Russian antihistamine that improves mitochondrial function, revealed that it preserved

cognition. This research was supported by Medivation Inc. Also, an 84-week study of Methylene blue (methylthioninium chloride), a refined version of a century-old antimalarial, interfered with the accumulation of tau tangles in the brain.

Exploring other approaches

Other studies investigated the effect of various nutritional supplements, immunotherapy, insulin and blood-sugar modifying medications. But because Alzheimer's is so complex, some predict that no single answer will address the problem. A "drug cocktail" that operates from several angles may be what it takes to truly ameliorate the condition.

"I suspect we're going to have to hit the pathways at multiple steps, kind of like combination chemotherapy for cancer," Dr. Gandy said.

An estimated 5.2 million people have Alzheimer's disease.

While experts say these studies hold much promise, they also are cautious because it is not unusual for drugs to fail as they are tested in bigger populations for extended periods.

Data presented on tarenflurbil, an anti-amyloid drug, are an example. Despite promising results in earlier studies, the therapy did not make a statistical difference in the cognition of 1,649 patients with mild Alzheimer's who were randomized to receive it or a placebo for 1½ years. Myriad Genetics Inc., the manufacturer, is discontinuing work on the drug. However, researchers said much was learned because it was the largest and longest trial of its kind.

"We've collected very valuable data on the progression of the disease in its earliest stages. We are confident that the results of this study will help researchers in their quest to develop new and better treatments," said Robert C. Green, MD, MPH, its lead author and a professor of neurology, genetics and epidemiology at Boston University School of Medicine.

Diagnostic tool needed

But investigators said their work is hampered by the lack of a definitive diagnostic test. The disease is now diagnosed and assessed by cognitive testing. This approach can lump other types of dementia in with Alzheimer's and confound results, as drugs and other interventions that address this disease's underlying mechanisms don't help those who have been misdiagnosed. In addition, current scales to measure cognition may not be sensitive enough to detect small changes in the short period covered by many early stage trials.

"This is a continuing question in Alzheimer's research. How do you monitor people's progress?" asked Donald Schmechel, MD, lead author of the paper on AL-108 and professor of psychiatry at Duke University Medical Center in North Carolina. He has received grants and research support from Allon.

5.3% of people older than 70 will develop at least mild cognitive impairment.

To address this issue, a push is under way to identify biomarkers that may lead to more conclusive diagnostic testing and monitoring. Studies presented involved measuring various proteins associated with brain amyloid in spinal fluid and those proteins involved in lymphocyte growth in blood.

Experts hope this work will lead to tests that will enable a diagnosis before symptoms ever appear, because they usually don't show up until significant damage has occurred. Presymptomatic diagnosis also could overcome the possible cause of some clinical trial failures. The drug may have been able to benefit a patient early on, but the therapeutic window has been missed.

"There has been a focus on moving the detection threshold earlier and earlier into asymptomatic individuals. To accomplish that, we need biomarkers to tell who is at greater or lesser risk as people age," said Ronald Petersen, MD, PhD, vice chair of the Alzheimer's Assn.'s medical and scientific advisory council.

To that end, researchers also are taking a closer look at patients with the earliest form of detectable dementia: mild cognitive impairment. Not everyone in this category might progress to Alzheimer's, but it is regarded as a significant risk factor.

The number of people with this condition also is large and growing. A paper presented by Dr. Petersen found that approximately 5.3% of those older than 70 will develop mild cognitive impairment; rates are higher for people who are older or male.

ADDITIONAL INFORMATION:

Working to save the Alzheimer's brain

An analysis based on 2001 data by researchers at the University of North Carolina at Chapel Hill offers insights into how significant scientific advances could have an impact on disease projections through 2050. The numbers represent millions of people expected to have Alzheimer's disease based on various scenarios. Relying on more recent data, the Alzheimer's Assn. estimates that 5.2 million people are living with this illness.

	If no significant advances occur	If advances delay onset	If advances slow disease progression	If advances delay onset and slow progression
2005	2.70	2.70	2.70	2.70
2010	3.14	3.14	3.14	3.14

2015	3.58	2.76	3.59	2.76
2020	4.09	2.78	4.11	2.81
2025	4.70	3.11	4.75	3.13
2030	5.54	3.62	5.60	3.66
2035	6.63	4.29	6.70	4.33
2040	7.88	5.01	7.97	5.07
2045	9.12	5.71	9.23	5.77
2050	10.21	6.31	10.33	6.39

Source: *Annual Review of Public Health*, May 2002

Search on for way to assess Alzheimer's risk

A mixture of lifestyle, cognitive issues and genetic factors appears to combine to create Alzheimer's disease, according to studies presented at the Alzheimer's Assn. International Conference on Alzheimer's Disease in Chicago, July 26-31. Researchers want to define these variables and assess their magnitude to devise a means for physicians to measure a patient's overall risk.

For instance, one study found that people living in a committed relationship at middle age cut by 50% their risk of cognitive impairment as they got older. Those who were widowed and did not remarry had the highest risk. Researchers theorized that the challenges of living with someone create a cognitive reserve protecting the brain. Losing a partner, however, could traumatize the brain. Continuing to live alone would not provide the cognitive resources needed to recover.

"Living in a couple relationship is normally one of the most intense forms of social and intellectual stimulation. If social and cognitive challenges can protect against dementia, so should living in a couple relationship," said Krister Håkansson, lead author and a researcher at the Karolinska Institute in Sweden.

Other studies implicated metabolic syndrome, severe head trauma, stroke, depression and cigarette use.

"Each of these risk factors has a low predictive value. We need to figure out which combination of risk factors has the best predictive accuracy," said Dr. Pieter Jelle Visser, a professor at Maastricht University in the Netherlands.

Another paper reported that physical activity could preserve brain volume, reduce falls and improve the quality of life of those with Alzheimer's.

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Alzheimer's Assn. International Conference on Alzheimer's Disease, Chicago, July 26-31
(www.alz.org/icad)