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Alzheimer's Payday Eludes Drugmakers

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Heroic failures -- that's how medical data firm IMS Health described the quest to find a cure for Alzheimer's disease.

That was four years ago, when there were two drugs available in the U.S. and another was about to reach the market. Now there are five drugs, including one that is rarely used because of its troublesome side effects.

But none of these drugs cure or halt the disease in which brain cells deteriorate and die, robbing people of their memory, their ability to function and eventually their lives. Today's drugs "only delay its progression, usually for months at most, in a relatively small percentage of people," said Leila Eadie, a health care analyst for the London-based research firm Datamonitor.

Although research failures keep coming, companies keep trying. There are over 40 drugs in mid- or late-stage clinical trials and over 100 more in early stages of development. "It's likely that very few of these will actually make it to the market," said Eadie.

The next generation of Alzheimer's research is coming not only from big companies like **Merck** (MRK:NYSE) and **Eli Lilly** (LLY:NYSE) but also from less-than-household names such as **Neurochem** (NRMX:Nasdaq) and **Axonyx** (AXYX:Nasdaq).

Figuring the amount of private money devoted to research is as elusive as finding a treatment, but the Alzheimer's Association notes that the federal government spent about \$640 million in 2003 alone.

"What you have is lots of companies trying many, many different ways of attacking this disease," Eadie said. "It's because no one understands the disease mechanisms. But there's a lot of money to be made if someone can find a good treatment."

Anyone who hasn't lost a loved one to Alzheimer's cannot adequately understand the frustration surrounding this disease, a frustration that will be played out in more households as the population ages. An estimated 4.5 million Americans currently have Alzheimer's disease, more than double the number in 1980, according to research published last year in the Archives of Neurology. By 2050, the number could range from 11.3 million to 16 million. The association says studies show that as much as 10% of the population 65 years and older have the disease; that percentage jumps to 50% for people 85 and older. If a parent or sibling has the disease, you have a greater risk of developing the disease, too. Because the average patient will live eight years -- some can live 20 years or more -- there is a great unmet need for more and better treatments.

Frustration in the Lab

A number of compounds have looked promising, only to fail in late-stage testing because the drug

wasn't effective or because side effects outweighed potential benefits. "The major frustration in Alzheimer's research is that no treatment seems to have a big effect on the disease so far," Eadie said. "But currently, and for the near future, there just aren't going to be any drugs that offer real hope to an Alzheimer's patient."

To understand the vexation of research, investors need look no further than Aug. 31, when **Forest Laboratories** (FRX:NYSE) reported that a late-stage clinical trial of the drug neramexane failed to achieve its goals. Patients given neramexane in combination with a drug already on the market did no better than patients receiving the marketed drug.

The findings were "unexpected," said Ian Sanderson of SG Cowen in a research note the day after the results were announced. "Our clinical consultants had anticipated a positive result."

These consultants, other medical experts and many analysts were stunned, because neramexane is similar to -- but more powerful than -- Namenda, the Forest drug approved 11 months ago by the Food and Drug Administration. (Both drugs are licensed from Germany's **Merz Pharmaceuticals**.)

The results are even more dispiriting because Namenda is the only FDA-approved drug for treating moderate to severe forms of the disease. The other drugs are acetylcholinesterase (AChE) inhibitors, which are approved for treating mild to moderate forms of the disease.

Forest, however, isn't giving up neramexane. It is enrolling patients with moderate to severe Alzheimer's disease in another clinical trial.

Namenda and neramexane attack the problem in a different way from the AChE inhibitors, which include Reminyl from **Johnson & Johnson** (JNJ:NYSE), Aricept from **Pfizer** (PFE:NYSE) and Japan's **Eisai**, and Exelon from **Novartis** (NVS:NYSE)

Cognex is rarely prescribed because of troublesome side effects. It was developed by **Warner-Lambert** -- which was acquired by Pfizer -- and is now sold by **First Horizon Pharmaceutical** (FHRX:Nasdaq).

AChE inhibitors prevent the breakdown of acetylcholine, a brain chemical that plays a key role in memory and other thinking functions. The drugs try to keep the levels of the chemical high despite the fact that cells assigned to making the chemical are being damaged or dying. About half of the people who take these drugs "experience a modest improvement in cognitive symptoms," says the Alzheimer's Association.

Namenda takes a different approach. Known as an N-methyl-D-aspartate, or NMDA, receptor antagonist, it seems to work on a different brain chemical called glutamate. This chemical plays a role in processing, storing and retrieving information. The brain needs a careful balance of this chemical, because too much glutamate is thought to lead to damaged nerve cells observed in Alzheimer's disease, the company says. Namenda appears to block the toxic effects of too much glutamate, allowing cells to function normally. "Although Namenda helps treat the symptoms of Alzheimer's disease in some people, there is no evidence that it changes the underlying nature of the disease," the FDA says.

Researchers are looking for ways to attack the disease rather than modify or delay its symptoms. One target is amyloid plaque, which is caused by toxic proteins called beta-amyloids. Because scientists believe the plaque kills brain cells in Alzheimer's patients, they want to stop the plaque from developing, and that means blocking the beta-amyloids from sticking to each other to create the plaque.

One potential beta-amyloid battler is Alzhemed, made by the Canadian company Neurochem. "We believe Alzhemed is the most promising Alzheimer's disease drug currently in development for the underlying cause" of the disease, said Matt Geller of CIBC World Markets, in a report last month to clients. "Alzhemed ... is a disease-modifying drug. We believe this is a key distinction from existing therapies." He has a sector outperform rating on the stock. (He doesn't own shares, but his firm co-managed a public offering and has an investment banking relationship.)

Geller noted that Neurochem expects to complete enrollment by year-end of a pivotal phase III clinical trial -- the last stage before an application is made to the FDA. The trial is enrolling patients with mild to moderate versions of the disease. "Previous data suggest that mild patients respond best to treatment," said Geller, adding that the drug is being developed as an add-on treatment to existing medications. A phase III test in Europe is scheduled to begin in early 2005. A best-case scenario would put the drug in the U.S. market during the second half of 2007.

New York-based Axonyx is testing the drug Phenserine, which takes a two-pronged approach: It's an AChE inhibitor, like most drugs on the market, but it also affects plaque formation. Early tests show the drug can inhibit production of the beta-amyloid protein, which leads to the development of plaque in the brain. "Phenserine [is] a potential breakthrough for Alzheimer's," said Elemer Piros, of the Rodman & Renshaw investment banking firm, in a report to clients last month. Phenserine compares favorably with the AChE drugs already on the market, he said.

Because "it appears to inhibit amyloid production," Piros said, the drug "may slow down or could even halt disease progression." (He has an outperform rating on the stock. He doesn't own shares, though his firm has had an investment banking relationship with Axonyx.)

Piros said the research showdown could come in the first quarter of 2005, when the company is expected to announce results of a phase III clinical trial measuring beta amyloid levels. "Should Phenserine alter beta amyloid levels, there would be a strong indication of disease-modifying activity," he said.

If not, it could be another heroic failure.
