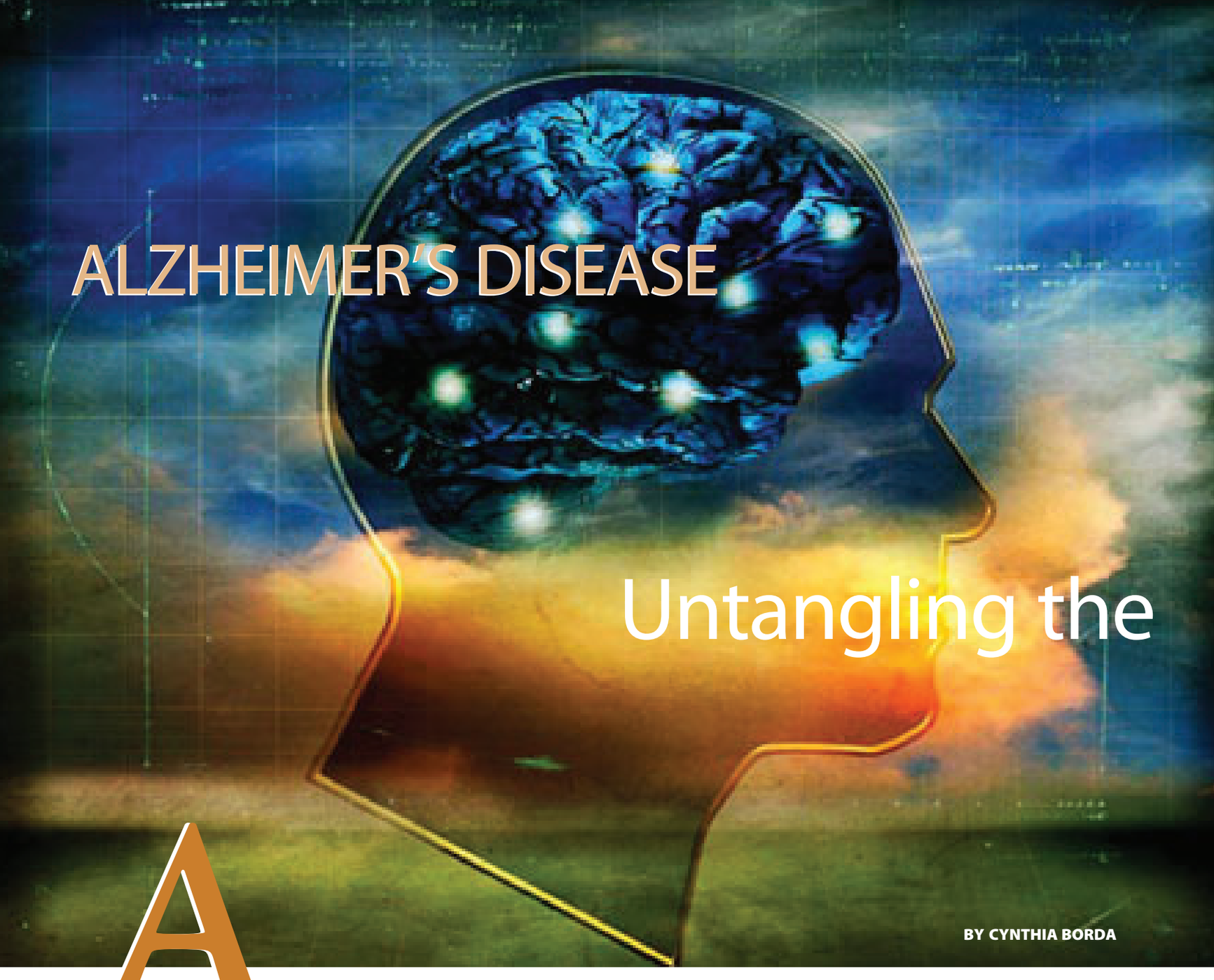


ALZHEIMER'S DISEASE

Untangling the

BY CYNTHIA BORDA

As the population ages, the prevalence of Alzheimer's disease (AD) is expected to increase. But there is no real way to diagnose the disease and drugs currently on the market only treat the symptoms of Alzheimer's.

At the same time, analysts say there is tremendous opportunity for pharmaceutical companies in this market, especially for companies that develop therapies that prevent neurological damage and cognitive decline. Drugs that can modify the disease will represent a breakthrough in this market.

AD is a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate, and carry out daily activities. There are four particular characteristics that define AD. They are: loss of neurons (especially cholinergic neurons); cortical atrophy, degeneration, or withering of cerebral cortex; presence of neurofibrillary tangles (NTs); and accumulation of neuritic plaques (NPs).

Alzheimer's primarily affects people older than 60, and as baby boomers are reaching this milestone AD is becoming a significant healthcare burden. According to the Alzheimer's Disease Education and Referral Center (ADEAR), which is a service of the National Institute on Aging (NIA), the current U.S. population with AD is 4.5 million. Without intervention, this number is expected to increase to more than 13 million by 2050.

There are a number of challenges associated with AD. To date, there is no cure and no one diagnostic tool that definitively diagnoses the disease. Additionally, there are a number of confounding factors that are implicated as the cause of AD. Therefore, researchers are grappling with the challenge of whether the elimination of one factor causing AD is enough, or do all the factors need to be addressed. Another challenge is educating physicians to recognize, diagnose, and subsequently treat the disease.

According to a 2005 report from Millennium Research Group (MRG), the number of people with AD in the global market (United States, France, Germany, Italy, Japan, Spain, and the United Kingdom) was 8.5 million in 2004. Of these, just less than half were diagnosed. Part of the problem is being able to recognize AD in the early stages, which can often be mistaken for other conditions.

"Diagnostic tools can be useful for detecting and diagnosing early stages of Alzheimer's disease, as well as for developing surrogate markers to help us determine drug effectiveness in clinical trials," says Neil Buckholtz, Ph.D., chief of the Dementias of Aging

DESPITE ADVANCES over the last decade in treating **ALZHEIMER'S DISEASE**, there is still a need for a way to **DIAGNOSE THE DISEASE EARLIER** and for therapies **THAT SLOW THE COURSE** of the disease. **PRODUCTS IN LATE-STAGE DEVELOPMENT OFFER SOME HOPE.**

BRAIN'S MYSTERY

Branch of the Neuroscience and Neuropsychology of Aging Program at the National Institute on Aging, which is part of the National Institutes of Health.

"The challenge of developing a product is largely a scientific issue," says Naissan Vahman, a senior analyst with MRG. "There are multiple reasons why patients develop AD; there is no clear composition, and there is no clear agreement within the scientific community."

But with these challenges come opportunities. Companies are vigorously conducting research that targets major factors in AD. There are also emerging companies that are researching either diagnostic tools for AD, preventive methods such as vaccines, or gene therapy.

THE CURRENT AD MARKET

The global market for AD products generated almost $3 billion in sales in 2004, according to Espicom Business Intelligence. This revenue makes it the second-largest neurodegenerative market behind multiple sclerosis. Of this $3 billion in sales, more than half is attributed to sales in the United States.

MRG predicts the Alzheimer's disease drug market in the United States, Europe, and Japan will increase by 15% annually for the next five years, reaching $5.5 billion by 2009. Further analysis by MRG breaks down revenue by the mild-to-moderate treatments and the moderate-to-severe treatments. The mild-to-moderate treatments are the acetylcholinesterase inhibitors (AChEIs), which had global sales of more than $2.0 billion in 2004. The moderate-to-severe treatments are the oral forms of memantine, which accounted for more than $400 million in global sales in 2004. The AChEIs remain the mainstay of treatment for AD. They are believed to work by inhibiting the breakdown of acetylcholine, thereby increasing available levels of this chemical in the brain. There is an established association between the loss of acetylcholine, a brain chemical involved in memory and thinking, and Alzheimer's disease.

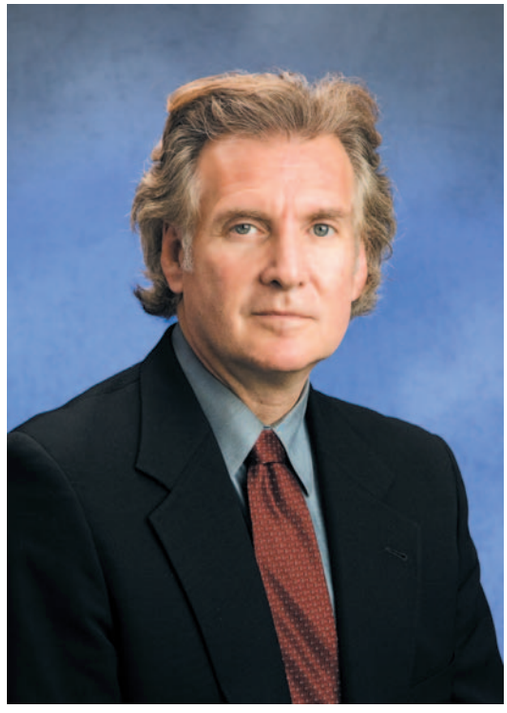
The three most prescribed AChEIs in the United States are Eisai/Pfizer's Aricept (donepezil), Novartis' Exelon (rivastigmine), and Johnson & Johnson/Shire's Razadyne (galantamine). Another product that is available is Cognex (tacrine). Cognex was the first AChEI approved in the United States. It was originally marketed by Warner-Lambert (now part of Pfizer) but because of a cumbersome four-times-a-day regimen, as well as liver toxicity issues, it is no longer a major player.

Eisai is the leader in the anti-AD market, with global sales of Aricept reaching more than $1 billion in 2004 and accounting for more than 50% of the market. According to market analyses by both MRG and Espicom, this No. 1 positioning is a result of being first on the market for once-a-day dosing, efficacy, and its strategic positioning by Pfizer.

"Eisai developed a copromotion relationship with Pfizer that has proven to be a successful marketing strategy," Mr. Vahman says.

The product is approved for treatment of mild-to-moderate AD, and Eisai is seeking approval for the treatment of severe AD. In October 2005, however, the FDA did not accept Eisai's supplemental NDA because of deficiencies in the format of the application.

Aricept ODT, an orally disintegrating tablet, is a new formulation that was made



DR. NEIL KURTZ

If we could diagnose AD earlier, we could start treatment earlier. EARLY TREATMENT COULD STABILIZE THE DISEASE.

available this year for patients who have difficulty swallowing.

According to Cheryl Barton, Ph.D., an analyst and consultant to Espicom, Novartis is in second place with its drug Exelon for mild-to-moderate Alzheimer's. Global sales in 2004 were $422 million, or roughly 14% of the market. Exelon is promoted as not only an AChEI but as a butyrylcholinesterase inhibitor (BuChEI). Since there is evidence that as AD progresses so do the levels of BuChEI, the dual inhibition with Exelon may play a role in the long-term progression of AD. The side effects of the AChEIs are similar, but Exelon is not metabolized by the liver, and, therefore, minimal drug interactions occur. This may be particularly important for the elderly on multiple medications. Novartis is developing a transdermal patch formulation of Exelon, as well as a modified-release version.

Razadyne (formerly known as Reminyl) is marketed by Johnson & Johnson's Ortho McNeil Neurologics division and Shire for mild-to-moderate AD. This AChEI has 10% of the global market, or $289 million in sales in 2004. The dual-action drug is an AChEI and an allosteric modulator of nicotinic cholinergic receptors (it enhances the response of these receptors to acetylcholine stimulation, although galantamine itself cannot stimulate the receptor).

Another currently available product is Namenda (memantine), which is the only commercially available drug approved for treating moderate-to-severe AD in the United States. Oral memantine was first developed by Merz Pharmaceuticals in Germany. Memantine is globally marketed under two other trade names: Ebixa and Azura. Namenda is marketed in the United States by Forest Pharmaceuticals. It is an N-methyl-D-aspartate (NMDA) receptor antagonist. By blocking the NMDA receptor it allows for some symptomatic improvement in cognition. Global sales in 2004, according to market analysts were $400 million, or 13% of total AD sales. This represents a 426.1% growth from 2003, according to MRG analysis.

Researchers from Espicom say Namenda/Ebixa/Azura will become more widely accepted and begin to address the high unmet clinical need in severe Alzheimer's.

DR. ERIC KARRAN

THERE IS A HUGE BODY OF EVIDENCE, BOTH PATHOLOGICAL AND GENETIC, that implicates the production of a small, relatively insoluble peptide, known as A-beta, in the pathology of Alzheimer's disease.

THERAPEUTIC DEVELOPMENT

"Companies are investing heavily in the development of AD products, and we are beginning to see some advances in this area," Dr. Barton says. "Researchers are now starting to understand the molecular basis, which will provide new targets to develop novel treatments."

But there are some challenges in getting an AD therapeutic product to market.

The first issue is diagnosing the patient, says Neil Kurtz, M.D., CEO and president of TorreyPines Therapeutics.

"The likelihood is that by the time AD is recognized, the pathology has advanced to a point where we are limited in what we can do for patients," he says. "In other words, treatment starts too late. The second issue is that the outcome measures that are used to evaluate the effectiveness of a drug are not as objective as they should be, such as with diabetes, or cancer. So evaluations are variable both clinically and in research. But we are making advances."

In addition, according to Andrea S. Witt, Ph.D., analyst for Decision Resources Inc., companies not only have to show efficacy and safety, but with subjective endpoints such as neuropsychological testing, it is very difficult to show disease modification.

"Therefore, the trials need to be large and long enough to show disease-modification, which can get very expensive for smaller drug companies," Dr. Witt say. "Sometimes these companies are limited to shorter trials where it is very difficult to show disease-modification. They can only show symptom relief. On the flipside, side effects are a big concern particularly in the frail AD patient. Since a lot of early stage clinical development is in young healthy volunteers, which do not reflect the outcome of an AD patient, there have to be additional safety trials on normal elderly patients."

Nonetheless, according to analysts, there are some promising products on the horizon.

ABOUT ALZHEIMER'S DISEASE

- An estimated **4.5 million Americans have Alzheimer's disease (AD)**. The number of Americans with AD has more than doubled since 1980.
- The number of Americans with Alzheimer's disease will continue to increase. **By 2050**, the number of individuals with AD could range between **11.3 million** and **16 million**.
- The average **lifetime cost of care** for an individual with Alzheimer's disease is **$170,000**.
- More than **seven of 10 people** with Alzheimer's disease **live at home**, where family and friends provide almost 75% of their care.
- By 2010, **Medicare costs for beneficiaries** with Alzheimer's are expected to **increase 54.5%** to **$49.3 billion** from **$31.9 billion** in 2000.
- **Medicaid expenditures** for residential dementia care **will increase 80%**, to **$33 billion** in 2010 from **$18.2 billion**.
- Alzheimer's disease **costs American businesses $61 billion a year**. Of that figure, **$24.6 billion** covers **Alzheimer's healthcare** and **$36.5 billion** covers costs related to caregivers of individuals with AD, including **lost productivity, absenteeism, and worker replacement**.

Source: Alzheimer's Association, Chicago. For more information, visit alz.org.

DR. NEIL BUCKHOLTZ

Diagnostic tools can be useful for detecting and diagnosing early stages of Alzheimer's disease, AS WELL AS FOR DEVELOPING SURROGATE MARKERS TO HELP US DETERMINE DRUG EFFECTIVENESS IN CLINICAL TRIALS.

Most predictions estimate the earliest entry of a novel product to be late 2007, with most products coming to fruition after 2010. Two products that show the greatest potential in terms of first to market are Neurochem's Alzhemed and Myriad Genetic's Flurizan.

Researchers with Espicom predict new Alzheimer's drugs could generate global sales of more than $550 million by 2010.

Alzhemed is an anti-amyloid that is expected to modify the course of AD on two levels. It is an orally administered, small organic molecule that has been specifically designed to modify the course of Alzheimer's. It is expected to prevent and stop the formation and deposition of amyloid fibrils in the brain, as well as bind to the A-beta-protein to reduce the amyloid-induced toxicity. There is currently a Phase III study being conducted for mild-to-moderate AD patients in the United States and Canada. A European-based trial is expected to begin recruitment presently.

The second promising drug on the horizon is Flurizan (R-flurbiprofen), a nonsteroidal anti-inflammatory (NSAID) that is being developed by Myriad Genetics. It has shown a reduction in beta-amyloid levels in the laboratory and animals. It is a selective amyloid lowering agent (SALA) that reduces levels of the toxic peptide amyloid beta 42 (Ab42) in cultured human cells and in animal models. Ab42 is a toxic peptide that kills neurons (brain cells) and initiates the formation of senile plaques in patients with Alzheimer's disease. Phase III trials have been started in patients with mild-to-moderate Alzheimer's disease.

Another product that has received attention is Lilly's LY450139. It has been in clinical development since late 2000 for mild-to-moderate Alzheimer's. This drug has demonstrated a reduction in levels of A-beta-peptide, along with good tolerability.

An explanation of the disease's pathology was summarized by Eric Karran, Ph.D., chief scientific officer of the Neurodegenerative Diseases Drug Hunting Team at Eli Lilly.

"There is a huge body of evidence, both pathological and genetic, that implicates the production of a small, relatively insoluble peptide, known as A-beta, in the pathology of Alzheimer's disease," Dr. Karran says. "This body of evidence has been coined the Amyloid Cascade hypothesis, which argues that the production and deposition of this peptide in extracellular deposits, known as plaques are ultimately responsible for the neuronal death and associated dementia that characterizes

DR. CHERYL BARTON

Companies are investing heavily in the development of AD products, and we are now beginning to see some advances in this area. RESEARCHERS ARE NOW BEGINNING TO UNDERSTAND THE MOLECULAR BASIS, WHICH WILL PROVIDE NEW TARGETS TO DEVELOP NOVEL TREATMENTS.

Alzheimer's disease. The production and clearance of the A-beta peptide are clearly important potential points for pharmacological intervention. In terms of production, A-beta peptide is excised from a larger protein by the sequential action of two proteinases: Beta Amyloid Converting Enzyme (BACE) and gamma-secretase.

"Our approach in this area is to seek inhibitors to BACE and gamma-secretase," Dr. Karran continues. "Our gamma-secretase inhibitor, LY450139, has been in clinical development since late 2000. Dose finding studies have shown highly reproducible reductions in A-beta in blood, along with very good tolerability thus far. These evaluations will allow initiation of a longer-term true efficacy trial that will assess the effect of this drug on the rate of progression of the disease. We are also seeking antibodies that bind A-beta and act to deplete the brain of that peptide, a concept that we are testing in Alzheimer's patients. We believe that for drugs that we hope will alter the course of the disease, early treatment is going to give patients the best opportunity for favorable clinical outcomes. Therefore, all of our early clinical efficacy studies will be in patients with mild-to-moderate Alzheimer's disease. It is too early to tell whether these approaches will be efficacious in patients with more advanced forms of the disease. The first objective is to find safe agents and get them into patients to find out."

Espicom Business Intelligence cited another promising product, Axonyx's phenserine for mild-to-moderate Alzheimer's. It is a dual-action compound that inhibits both acetylcholinesterase and beta-amyloid precursor protein. Plans are under way to reformulate phenserine to an extended- or sustained-release formulation. Phase III trials are ongoing.

Beta-amyloid protein is an area receiving a lot of attention in other research efforts. Other hopes are being hung on anti-inflammatories and anti-oxidants as possible therapies.

"These compounds make sense because there is evidence to support both inflammation and oxidative stress in the AD brain," Dr. Buckholtz says. "Unfortunately, there have not been beneficial results seen with these compounds to date."

According to the MRG market analysis, other areas of research include neuroprotective and neurotrophic compounds, beta-secretase inhibitors, phospholipids compounds, L-type calcium channel modulators, phosphodiesterase 4 compounds, ampakine compounds, and protein deposition inhibitors.

"A key to new products is to show safety," Dr. Witt says. "They do not even have to show significant superiority to the AChEIs; they have to mostly show they are safe for the patient."

In fact, most experts believe any emerging therapy will be used in combination with existing products.

"The AChEIs have made a significant impact in the AD market, there is no reason not to use combination therapy using new compounds with these existing products," Dr. Kurtz says.

Dr. Barton concurs. "Any novel treatment that is well-tolerated may be monotherapy, but there is every reason to look at these therapies in combination," she says.

DIAGNOSTIC DEVELOPMENT

Diagnostic-tool development is a hot area in the AD market, experts say.

"Much of the innovative science being conducted in AD research is to seek ways of monitoring disease progression by using biomarkers that will assist in clinical trials," Dr. Karran says.

The other use for diagnostic tools is to identify AD as early as possible.

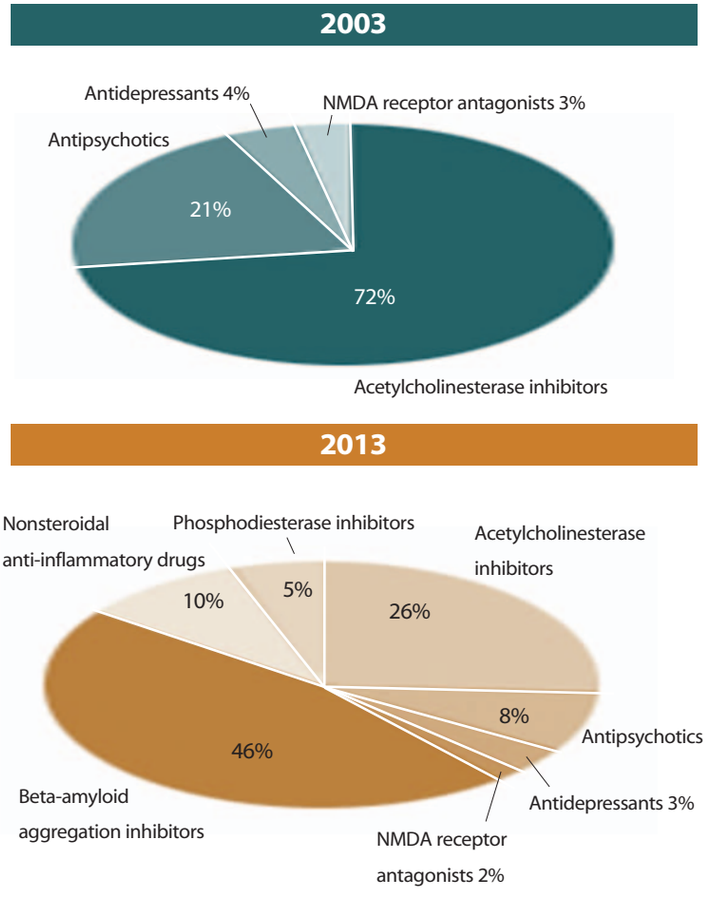
"If we could diagnose AD earlier, we could start treatment earlier," Dr. Kurtz says. "Early treatment could stabilize the disease."

Dr. Buckholtz notes that two areas are being actively studied for diagnostics: neuroimaging and biological markers in blood, urine, and spinal fluid.

One compound that is being researched as a biomarker is Pittsburgh Compound B being developed by GE Healthcare. It is an imaging agent that was licensed by the company from the University of Pittsburgh in 2003. GE Healthcare is currently developing targeted molecular diagnostics for a variety of neurological diseases, including Parkinson's disease and AD. It works by binding to the abnormal amyloid plaque in the brain. When imaged with a positron emission tomography (PET) scan, this compound shows researchers actual pathological changes in the brain that could turn out to be the best and earliest signs of the disease.

Dr. Witt predicts this could be on the market in 10 years to 15 years.

ALZHEIMER'S DISEASE THERAPIES MARKET SHARE



Source: Decision Resources Inc., Waltham, Mass. For more information, visit decisionresources.com.

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NAISSAN VAHMAN

THE CHALLENGE OF DEVELOPING A PRODUCT IS LARGELY A SCIENTIFIC ISSUE. There is no clear composition, and there is no clear agreement within the scientific community.

GE Healthcare began collaborating with Lilly for this project in April 2005. GE Healthcare has access to Lilly's extensive molecular libraries to search for compounds that would be promising for use in targeted diagnostic imaging agents for AD. Lilly will then have access to any diagnostic agents developed by GE under this collaboration to use in discovery, development, and validation of Alzheimer's disease therapeutics from the early-research phase through clinical trials.

GE also is collaborating with Roche, an alliance that began in July 2005. In trials, patients taking a Roche anti-amyloid drug candidate are being monitored for drug response using GE's PET diagnostic imaging agent.

Scientists at Northwestern University announced this year the detection of amyloid beta-derived diffusible ligands (ADDLs) using technology they developed, BCA or bio-barcode amplification. This BCA technology is able to detect these proteins, which are only five nanometers wide and found in very low concentrations in the cerebrospinal fluid. Science has supported the theory that ADDLs accumulate at the beginning of AD. The next step is to try the technology using urine or blood, since sampling of cerebrospinal fluid is very invasive.

TorreyPines Therapeutics has a two-pronged approach to AD research. The company's product, NGX267/NGX292, has a dual mechanism for treating AD. It stimulates M1 receptors on intact cholinergic neurons to replace acetylcholine, and it lowers AB42 peptide. In addition, the company is in the business of gene discovery.

"If we can discover the gene, we might be able to figure out a way to diagnose, in addition to finding a molecule to treat," Dr. Kurtz says.

LOOKING TO THE FUTURE

Experts in the AD arena all indicate that the future is bright. There will continue to be growth for the AChEIs and Namenda. Research has provided the pharmaceutical industry with a greater understanding in the mechanisms underlying the progression of AD, resulting in the identification and validation of new targets, including new genes and anti-amyloid approaches. Researchers with Espicom believe products from these projects will drive the future growth in the AD market.

According to Dr. Barton, Aricept will benefit from its ORT formulation and the company is expected to pursue other indications. Exelon will gain market share with the release of the transdermal patch. Razadyne will give Aricept some competition with a once-daily formulation and one-year head-to-head trial data, where Razadyne shows superiority in two secondary parameters. Namenda, being the only product currently available for moderate-to-severe AD, will begin to be used more frequently in combination with the AChEIs.

"Preventive medicine is, of course, what everyone strives for," says Dr. Kurtz.

A vaccine is one preventive possibility. Several years ago a vaccine that was developed showed promise in mice. It was only when injected into humans that a serious side effect, encephalitis, was discovered. Research is continuing, and more recently, development of a nasal vaccine has begun.

Gene therapy also is being researched for AD. Currently, nerve growth factor is being studied as a way to slow down the progression. There are several hurdles to overcome with this therapy. One hurdle is the cost, another is that patients would require brain surgery.

"I and all of my colleagues are not complacent about the magnitude of the challenge," Dr. Karran says. "But I believe we have made some significant progress in advancing some very innovative approaches to clinical testing."

Dr. Kurtz agrees. "We should all be encouraged; the science is strong. I am very optimistic that we all should be able to make a difference. With great risks come great rewards," he says. ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

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