

# The Memory Pill: A Cure for Forgetfulness

Uta Maeda

Perhaps the idea of a memory pill sounds like something straight out of a science fiction movie. Given today's rapidly expanding medical frontier, the reality may actually be right around the corner. The field of neuropharmacology is currently undergoing a growing involvement in the development of a new class of drugs to help improve memory for individuals who are ill or aging. This effort mainly targets victims of Alzheimer's disease (AD), which affects 10% of people over the age of 65<sup>1</sup>. AD is characterized by an accumulation of insoluble protein called beta-amyloid, which forms a plaque that clogs the brain<sup>1</sup>. As a result, mental and physical functions gradually deteriorate, and victims die after ten to twelve years. The most significant consequence of AD is the loss of memory, which is one of the greatest worries in today's society of information overload. Pharmaceutical companies around the world continue to pour more effort and money into this battle, as billions of people await a solution to guard themselves against forgetfulness.

The development of such drugs requires a sophisticated understanding of the brain's memory mechanisms. After all, the pill must account for the ability of humans to remember events that occurred ten years ago, as well as where they put their car keys ten minutes ago. The processes of memory formation and consolidation are controlled by the hippocampus, a small structure in the brain resembling the shape of a seahorse. Consolidation is the process of converting short-term memory into long-term memory, and occurs when new synaptic connections between neurons become permanent or "engraved"<sup>3</sup>. Memory diseases result from the steady deterioration of this ability to form new long-term memories. Previously stored memories remain, but new memories cannot be consolidated. Tests show that memory declines steadily after age 25, and by late middle age, humans lose 1% of brain volume each year<sup>4</sup>. Currently, approximately 4 million Americans have AD, 12 million suffer from mild cognitive impairment (MCI), and over 76 million experience age-associated memory impairment (AAMI), characterized by mild forgetfulness<sup>2</sup>. As the anxiety and awareness of the baby boomer generation continue to rise, the pharmaceutical industry is scrambling to create a treatment for memory loss.

Why is the idea of this so-called "smart pill" just now taking flight? Considering how memory loss is not a new problem, one would wonder why every major drug company in the world has not already jumped to investigate this possibility. Researchers attribute the delay mainly to the lack of a real diagnostic target. By the time patients are diagnosed with AD, the damage has already progressed so much that any sort of treatment would be essentially useless. The Food and Drug Administration (FDA) ignited a whole new world of motivations for the development of memory drugs in the spring of 2000, by identifying a new warning category known as mild cognitive impairment (MCI), the fuzzy state that lies between normal midlife memory loss and the devastating decline of cognitive abilities caused by AD<sup>4</sup>. People suffering from MCI do not show deterioration in IQ scores, but experience a significant level of forgetfulness, such as being unable to remember recent conversations. Within six years of being diagnosed with MCI, over 80% of patients progress to AD<sup>1</sup>. On March 13, 2001, an advisory group of the FDA expressed its approval of experimental treatments for AD even if they cannot prevent the progressive course of the disease itself, as long as they can improve memory for MCI victims<sup>1</sup>. This decision was based on the notion that the best method of preventing AD may be to focus on fighting simple forgetfulness. Finally given a thumbs-up by the FDA, pharmaceutical companies all over the world set off on a race to create this "Viagra for the brain"<sup>2</sup>.

A drug for the brain is not an unfamiliar concept in today's society by any means. There are already many "lifestyle drugs" that are used for cognitive enhancement by the general public. Nicotine and caffeine are examples of proven memory boosters taken on a daily basis in order to improve alertness. Even sugar falls into this category; glucose provides fuel for neurons and is a key ingredient in the production of acetylcholine, a brain chemical that helps form memories. In our current society, the newly developing memory pills are far from obtaining government approval, but they are already creating a stir in the general public. Judging from the \$1 billion-a-year sales of the herbal medicine ginkgo biloba, it seems that consumers are not waiting around for an FDA approved drug<sup>2</sup>. Skeptics of this "smart pill" idea argue that these new memory drugs currently under investigation are no better than the substances we find on the breakfast table. In fact, studies conducted thus far show that spending money on memory-enhancing drugs like ginkgo biloba has just as much effect as a trip to Starbucks. Pharmaceutical companies are on a quest for a more effective pill that will go above and beyond the capacity of commonly found lifestyle drugs.

Companies currently use two main strategies in their battle against MCI and consequent AD. Their experimental drugs aim to either improve the brain's ability to form memories despite the buildup of amyloid plaque, or to delay the accumulation of the plaque itself. The first category includes a class of drugs called ampakines, pioneered by Cortex Pharmaceuticals. Their particular approach aims to amplify memory by increasing the activity of brain chemicals such as the neurotransmitter glutamate, which are important for memory formation<sup>1</sup>. Glutamate has a corresponding protein called the AMPA receptor. Upon repeated exposure

to glutamate within a short period of time, the AMPA receptor triggers another receptor called NMDA located at the same site. Calcium molecules enter the brain cell, and NMDA begins sending its signal. This admission of calcium causes the synaptic connection to change, and this is precisely believed to be the basis of memory formation and consolidation<sup>3</sup>. The new drugs attempt to boost the glutamate signal through the AMPA receptor, thereby causing the AMPA receptor to activate the NMDA receptor more quickly. This leads to easier memory encoding and promotes faster consolidation. Cortex's first ampakine, Ampalex, is in its second of three stages of clinical trials for AD and MCI<sup>3</sup>. NeoTherapeutics Inc. of Irvine, California, also aims to enhance memory with its drug Neotrophin, which stimulates the production and release of growth factors in the brain that stimulate neurons to make new connections with other neurons<sup>1</sup>.

Memory Pharmaceuticals and Helicon Therapeutics are working on drugs to help long-term potentiation, or the conversion of transient short-term memory into long-term memory, a process that is degraded by AD. The companies recognized the importance of cyclic AMP (c-AMP), a messenger molecule that helps form memories by stimulating proteins that strengthen the connections between neurons. The two companies also focused on developing a drug to enhance the power of CREB, which is a c-AMP response element binding protein. The more CREB in the neuron, the faster the long term memory is consolidated. C-AMP acts like the manager of the "memory factory" and activates CREB, which in turn initiates the "assembly line," or signal cascade, to produce long term memories<sup>3</sup>. The harder the factory manager works, the more efficiently and quickly products will be manufactured. Thus the goal is a drug that will either boost c-AMP and CREB levels in the brain or help slow the breakdown of c-AMP. Memory Pharmaceuticals also seeks to develop drugs that enhance the growth and power of undamaged neurons in the brain's memory centers<sup>1</sup>. This is an approach that could be useful for treating a wide variety of diseases besides AD, possibly helping re-engineer the memory circuitry of stroke victims or people with mental retardation.

Other companies are developing experimental vaccines that would stimulate the immune system to slough off the amyloid plaque deposits that accumulate to cause AD. Southern San Francisco's Elan Corporation, the leader in the development of this type of drug, achieved a 70% reduction of plaque in the brains of mice that were genetically engineered to develop AD<sup>1</sup>. According to Dr. Leon Thal, the head of the Alzheimer's Disease Research Center at UCSD, if such drugs could delay the onset of AD for just one year, it could save \$10 to \$20 billion and treat between 220,000 and 440,000 people each year<sup>1</sup>.

The development of a memory pill is a risky business, and its potential emergence into society carries many ethical

implications and consequences. Perhaps the biggest question raised by society is: "Is this cheating?" Although it is meant as a drug to treat medical conditions, it could easily become a lifestyle drug like caffeine. Drugs like Provigil have taken this course: although it is intended as a treatment for narcolepsy to prevent drowsiness, there are many cases of its off-label use as a just-for-fun energy booster by consumers who want to be able to sleep less, stay up later, work harder, and play more<sup>2</sup>.

"No one thinks twice about spending to correct age-related body changes affecting the hair, the eyes, bones, skin, even erectile dysfunction," says Steven Ferris, executive director of the Silberstein Aging and Dementia Research Center at the New York University School of Medicine. "Why should the brain be any different?"<sup>5</sup>. Others, such as Tim Tully of Cold Spring Harbor Laboratories, argue that it is just as necessary for humans to forget as to remember<sup>5</sup>. Otherwise, the memory pill may help patients retain useless information such as the color of the shirt worn by their spouse last Thursday, cluttering their brains and making it difficult to remember more crucial information.

Will a memory pill cause performance standards to rise, leaving people who cannot afford the drug out in the dust? Will the consumption of the pill be required for people who make life-death decisions, such as pilots, surgeons, and top officials at intelligence agencies? All these and more are unanswered questions that must be addressed as the experimental drugs inch closer to FDA approval.

The creation of the ultimate panacea memory pill still remains far from plausible. Such an ideal drug must account for the many different types of memories that the human brain is capable of forming. These include, but are not limited to: motor programs for storing information for basic functions like tying shoelaces, semantic memories for understanding the nuances of language, high-level explicit memories for telling life stories and sharing personal experiences, and memory programs for assimilating new things such as learning faces and names. The concept of a memory-enhancing pill appeals to companies and consumers, because it is a step toward a more tempting goal: increasing intelligence. The pharmaceutical industry is enticed by the fact that "from great anxieties come great profits"<sup>3</sup>. Although originally a treatment aimed at the elderly population suffering from memory loss, the drug target will inevitably migrate toward the middle-aged population who just want to "tune up" their memory. In this era when drugs are no longer only for treating disease, it is certain that memory pills will make an enormous impact when they plunge into the market and change the capacity of the human brain in ways never thought possible.



## References

1. Freundlich Naomi. "Arresting Alzheimers; Drugs that fight milder memory loss may prevent its onset." *Business Week* 2001; 3736: 94-97.  
 2. Hall Stephen S. "The Quest for a Smart Pill." *Scientific American* 2003; 289.3: 54-65

3. Plotz David. "Total Recall—The Future of Memory." *Slate* 2003; <<http://politics.slate.msn.com/id/2079202>> (2 Oct. 2004).  
 4. Stipp David. "A Pill to Help You Remember." *Fortune* 2001; 144.9: 162-167  
 5. Talan Jamie. "Insufficient memory: can a pill boost your brain's ability to hold information?"

*Newsday* 2003; [http://www.cognitiveliberty.org/dll/memory\\_drugs\\_newsday.html](http://www.cognitiveliberty.org/dll/memory_drugs_newsday.html)> (20 March 2005).