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# Memory and the Older Woman: Diagnosis and Treatment

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## Introduction

Memory is as vital to us as is breathing. When our memory no longer works perfectly, it can be an alarming occurrence. Consider the following case:

*Case 1. A 65-year-old woman locks her keys in her car. She becomes upset, convinced that she was forgetting more than she did previously. At the same time, she carries out all of her normal daily activities without any difficulties; this includes volunteering two days a week at a hospital and serving as the secretary of her church group. In the course of these activities, no one else observes difficulties with her memory.*

While a change in memory can be alarming, there is a widely held view that growing older inevitably leads to impaired memory. Some older individuals might lower their expectations with regard to their memory function. Consider a second case:

*Case 2. A 72-year-old woman is noted by her family to repeat herself in conversation. On several occasions she becomes upset with her husband because he claims that she failed to remember conversations they had had. The woman feels that her difficulties are no greater than anyone else's her age.*

These two cases illustrate the challenges inherent in understanding

memory complaints in older individuals. Some memory lapses are normal. Memory function is highly susceptible to mood, expectation and confidence. In this era of increased awareness about Alzheimer's disease, some people might become overly upset about any signs of forgetfulness, even within normal limits. Yet, like the woman in the first scenario, there might be no actual changes in the brain that are responsible for memory lapses. However, memory loss in an older woman, as in the second case, might indicate an incipient brain disorder. This is because dementia-causing illnesses become increasingly common in the eighth, ninth, and tenth decades of life.<sup>1</sup> Dementia, the syndrome in which difficulties with learning new things and short-term forgetfulness are dominant symptoms, affects 7%-10% of individuals over age 65.<sup>2</sup> Among people over age 85, 30% to 40% of people have some degree of dementia.<sup>2</sup>

This article seeks first to explain the differences between normal forgetfulness and dementing illness, and then to address emerging treatments for dementing illnesses. At present and for the foreseeable future, there are no medical treatments to enhance memory function in people with normally functioning brains. There are, however, common-sense approaches to enhancing everyday memory. These approaches are often ignored because they require some discipline to use.

## Ups and Downs of Normal Memory Function in the Older Woman

For normal mental activities, and memory in particular, it is well known that sleep deprivation, ongoing health problems, depression, or preoccupation with major life stressors can degrade performance. In terms of memory, batting averages serve as an illustration. Just as a baseball player at the top of his game might have a batting average of .333, whereas a struggling player might have an average of about .250, it is inevitable that a person experiencing depression is likely to be distracted, preoccupied, and have difficulty focusing on tasks and activities. She also is likely to lack energy and confidence in herself. As a consequence, it shouldn't be surprising that people with depression report poor memory and difficulty with concentration. Similarly, if a person is suffering from an ongoing medical illness, and perhaps experiencing pain or discomfort, memory function is likely to suffer.

Even without the existence of depression or other illnesses, our memories are still not photographic. As people age their rote memory ability almost certainly declines. Rote memory refers to the ability to acquire and then repeat a phone number, a long sentence or series of commands. Young people in their twenties are typically better than 60- and 70-year-olds at repeating back a string of digits—for example, an unfamiliar phone number—or following a conversation. That ability is particularly useful in acquiring a great deal of

information in a short period of time. Young students practice that skill constantly when studying for tests. Older people may be frustrated with their inability to comprehend a series of directions, and may feel too embarrassed to ask that the speaker to stop and repeat what he just said. However, an edge in rote memory isn't really necessary for effective memory in most daily activities. With a bit more time to learn something, someone with lesser rote memory skills can still learn and retain new information equally well. For example, rereading a memo might be more than sufficient to achieve the retention that someone with a photographic memory gains from a single reading. Moreover, in real-life activities, learning a large number of facts doesn't help very much if the facts can't be cast into a meaningful pattern. Applying insight, wisdom and experience to facts is what can actually improve with age. So, while rote memory in older individuals is not as efficient as it is in younger people, other mental functions that get better with age can more than help to compensate. Moreover, while older people feel as if certain details from the remote past may be lost to them, it is highly unlikely that isolated changes in remote memory ability are an indicator of brain disease.

A decrease in rote memory or remote memory is not a warning sign of brain disease. Nor is an occasional failure to retrieve seemingly well-known information like the name of a casual acquaintance or an occasionally used phone number. It is common, and normal, to occasionally misplace something. It is common to occasionally stumble over choosing the correct word in conversation. It is common to need reminders to carry out a complex task (if it is done infrequently), such as remembering rarely used recipes or little-used procedures on your computer.

Older people need to realize that forgetting is an expected part of daily life—regardless of age. When an individual experiences emotional stress

from trying to do too many things at once, or from worries about family, finances, health or interpersonal conflicts, memory inefficiencies will inevitably rise. Poor sleep also will degrade mental performance. These are potentially controllable and manageable factors. The woman in the first of our two cases had an ongoing problem with joint pain. She was receiving narcotic pain medications, which she took sparingly but regularly. After a visit to a rheumatologist, her medications were changed. The pain diminished. She realized she felt much better both physically and emotionally. Indeed, she did not have brain disease.

### **Strategies for Maintaining Cognitive Function**

Much has been written about ways to improve mental functions in older individuals. In the long run, a healthy diet, regular exercise and avoiding smoking offer obvious general health benefits by reducing the likelihood of obesity, diabetes and heart disease. There is a compelling argument for implicating heart disease as a risk factor for Alzheimer's disease, so that over the course of middle age and into adulthood, a healthy lifestyle might have benefits for both the heart and the brain. For the older woman, social and mental engagement almost certainly have more immediate beneficial effects on mood and probably on memory and other mental functions. Although it remains speculative as to whether mental stimulation can alter the neuronal architecture in the brain, it is clear that staying socially engaged as well as mentally stimulated improves attention, mental flexibility and probably short-term memory.

### **When is Forgetting Pathological?**

There are certain features of memory loss that raise concerns about incipient brain disease. One of the most important is whether a person asks questions over and over again in a short period of time. Unless a person has significant hearing loss, the repetition of questions

or observations is not something people without impaired memories normally do. Individuals with incipient dementing illness commonly misplace items. They commonly forget recent events and conversations, and have greater difficulty remembering the names of acquaintances. They may have trouble keeping track of the day or date—not just occasionally, but on a daily basis. They may forget appointments and be more likely to lose their train of thought in midstream. The key to understanding and recognizing memory problems that are due to a brain disorder comes in grasping that the person's skills and abilities truly differ from their prior level of functioning. Sometimes this difference is obvious to the family and to physicians. At other times, early in a dementing illness, the distinction between "same as always" and "definitely different" can be quite tricky. In the second case outlined earlier in this article, the woman's continued repetitions and forgetting of conversations strongly suggested an incipient dementia.

From the perspective of a neurologist, two actions are necessary to diagnose a memory disorder: (1) obtaining a detailed history of the memory complaint and failures in daily activities, and (2) performing an assessment of mental function, referred to as the mental status examination. To diagnose the disorder correctly, a physician must be able to speak to a knowledgeable informant, one who would have been in a position to observe whether the person with alleged memory problems exhibited any such behaviors. Through a series of questions, the nature of the memory lapses can be characterized, and it can be determined if those lapses fit the pattern of memory lapses seen in dementia.

Validating observations gathered from the person's history requires direct observation. That is where the mental status examination comes in. A mental status examination consists of a series of standardized questions about the date and time, as well as direct tests of memory, concentration, mental agility and

language. The mental status examination can be very helpful in clarifying the nature of memory problems. While the Mini-Mental Status Examination is the most widely used bedside exam, my colleagues and I at the Mayo Clinic prefer a different bedside test, the Short Test of Mental Status, because it is somewhat more sensitive to changes in people who are more mildly affected by memory problems.<sup>3</sup> The Short Test of Mental Status consists of a series of questions about orientation for time and place, digit span, arithmetic, fund of information, verbal similarities, drawing ability and recall after a delay. In more difficult circumstances, a more detailed assessment of memory and mental function may be needed; this is what is referred to as neuropsychological testing. When it is done properly, neuropsychological testing can quantitate and characterize memory function quite accurately. Neuropsychological testing is particularly useful in persons with milder problems. Neuropsychological testing refers to the standardized assessments of cognitive function that are performed by trained neuropsychologists using validated, reliable tests of memory, language, reasoning and attention.

A mental status test administered to the woman in the first case study had a normal result. If neuropsychological testing had been performed, it might also have shown preserved performance on tests of delayed recall of verbal or pictorial information. Mental status testing in the second woman was clearly abnormal. She was uncertain of the date and day of the week, and she misstated the year. After being instructed and drilled on remembering four words, she did not recall any of them 5 minutes later.

### **The Spectrum of Impaired Memory and Mild Cognitive Impairment**

If a woman's memory becomes impaired, loss of daily functioning does not occur immediately. The evolution of dementia is a very slow and variable process. In a typical woman with evol-

ing memory loss, everyday abilities may remain intact for some time. Eventually, those functions may be affected, but that could be several years after the first memory problems appear.

Mild cognitive impairment has gained considerable attention and interest in the last decade because it captures the transitional nature of the early stages of memory loss. Mild cognitive impairment is a transitional state between normal cognition and developing dementia.<sup>4</sup> Forgetting conversations and misplacing items are common complaints for persons with mild cognitive impairment. Preservation of daily living skills—from cooking, socializing, and managing simple financial transactions, to maintaining personal appearance—is evident. It is important to identify a person with memory problems in this setting. At the same time, the label of “dementia” is inappropriate because independence and autonomy may be largely preserved. Labeling them as having a more serious condition is not justified.

Another important aspect of the concept of mild cognitive impairment is that it could be a point of intervention. At the present time, there are no medications approved for treating mild cognitive impairment, but it is hoped that this will change in the next few years.

When that occurs, pharmacologic therapy for mild cognitive impairment will, no doubt, be more effective than such treatment that is initiated once full-blown dementing illness has developed.

### **Dementia versus Alzheimer's Disease**

The term “dementia” describes symptoms of memory loss that generally have a gradual onset and are of a worsening nature. An important stipulation in the definition of dementia is that a person's sensorium, or level of arousal, is normal. This is necessary in order to distinguish dementia from acute confusional states, also known sometimes as delirium. Dementia also implies that there is erosion of other mental functions, such as greater difficulties with

word-finding, reasoning, mental agility or problem-solving. These difficulties interfere with a person's independence. It is that loss of independence that is at the core of the concept of dementia, and is what distinguishes dementia from mild cognitive impairment. The woman in the second case profiled earlier in this article was beginning to have difficulty following recipes and keeping her checkbook. These features, combined with her memory difficulties, implied a diagnosis of mild dementia.

Alzheimer's disease is the most common cause of dementia in older people, constituting about 60% to 80% of all cases of dementia. There are other causes of dementia. Another important cause of dementing illness is cerebrovascular disease (stroke). That disorder is known as vascular dementia. The dementing illness that accompanies Parkinson's disease is also common. That disorder is sometimes known as dementia with Lewy bodies. Lewy bodies are microscopic features that are seen in the postmortem analyses of the brains of people who have succumbed to Parkinson's disease. These three disorders—Alzheimer's disease, vascular dementia, and dementia with Lewy bodies—account for well over 90% of dementing illnesses in older people. They often overlap with one another, so that Alzheimer's disease may often be present along with vascular dementia or dementia with Lewy bodies. From a therapeutic perspective, the possibility that Alzheimer's disease may be a contributor in vascular dementia or dementia with Lewy bodies offers the opportunity to use Alzheimer's medications in those other two diseases.

There are less common disorders that may cause or exacerbate dementia. These include a number of specific brain diseases such as brain tumors, chronic subdural hematomas and normal-pressure hydrocephalus. Dementia may also be caused, on rare occasion, by medical illnesses such as vitamin B12 deficiency or hypothyroidism. Part of

the medical evaluation of dementia involves laboratory testing directed at these other disorders.<sup>5</sup>

### Therapy for Alzheimer's Disease

Beginning in the 1980s, a very active approach to finding therapies for Alzheimer's disease developed. The first medications to be approved for the treatment of Alzheimer's disease were the cholinesterase inhibitors. There are currently three of them available in the United States: donepezil, galantamine, and rivastigmine. All are approved for the treatment of mild to moderate Alzheimer's disease. In this author's experience, donepezil and galantamine are reasonably well tolerated, while rivastigmine is often associated with intolerable gastrointestinal side effects.

Cholinesterase inhibitors have been shown to be effective in delaying the progression of symptoms in patients with dementia due to Alzheimer's disease. Unfortunately, they do not stop the progression of the disease in the brain. They are best described as able to treat symptoms, meaning that they slow down the worsening of the disease for a period of time. Despite their modest effects, this author believes that cholinesterase inhibitors are beneficial for Alzheimer's patients. Studies have shown that the benefit of these drugs comes from delaying the progression of symptoms. This is illustrated by the results of a study in which Alzheimer's patients were originally characterized based on their level of function in day-to-day affairs.<sup>6</sup> Study subjects were then assigned to receive either donepezil or a placebo. The goal of the therapy was to avoid decline of a significant nature. Patients treated with donepezil were less likely to experience a decline compared with the placebo group. Donepezil does not have a dramatic effect; however, because of the inevitable decline that occurs in Alzheimer's disease, realizing even modest beneficial effects is worthwhile. It would be this author's recommendation that the second woman in the

earlier scenarios be placed on a cholinesterase inhibitor.

A recent study has shown some benefits of donepezil in patients with mild cognitive impairment.<sup>7</sup> However, mild cognitive impairment is not yet an indication for these medications. The debate, which is yet to be played out, is whether initiating a drug like donepezil in a person with mild cognitive impairment makes more sense than waiting to use the medication in a more advanced condition. If the medication's benefits are limited and may not materially impact a person's level of functioning in day-to-day affairs, why not start medication when the person's functioning is at a high level?

At the beginning of 2004, a second class of medication became available for the treatment of Alzheimer's disease. Memantine was approved for the treatment of moderate to severe Alzheimer's disease. Memantine is a drug that alters the function of the brain chemical transmitter glutamate. It has been approved for use in conjunction with cholinesterase inhibitors in moderate to severe Alzheimer's disease.<sup>8</sup> However, it has not been approved for use in mild Alzheimer's disease at this time.

### Prospects for the Future

As yet, there are no therapies that are available for the prevention of Alzheimer's disease. Ideally, prevention of Alzheimer's disease would be far more effective than treating the disorder once it has produced symptoms. Unfortunately, large-scale trials of estrogen therapy (ET) failed to show its protective effects. The failure of the Women's Health Initiative Memory Study (WHIMS) to show such a benefit was a great disappointment to many.<sup>9</sup> Arguments have been made that the WHIMS enrolled women who were too old to benefit from the preventive effects of ET. That argument cannot be refuted at present, but based on the results of the study, ET cannot be recommended to prevent Alzheimer's disease.

In late 2004, a large prevention study of the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the prevention of Alzheimer's disease was terminated because of concerns about side effects of one of the agents. There is considerable interest in NSAIDs, but at the present time they cannot be recommended for use.

There are also ongoing studies on the use of vitamin E and Ginkgo biloba for Alzheimer's disease prevention, but results from these large, multiyear trials will not be available for several years.

Research on the basic science of Alzheimer's disease has evolved rapidly and with great success. There are very exciting leads for therapeutic interventions based on our emerging understanding of the biochemistry of the amyloid  $\beta$ -peptide.<sup>10</sup> This protein is thought to be a key molecule in the development of Alzheimer's disease. A vaccination has been tested, but unfortunately side effects cut a clinical trial short. Other approaches based on immunologic strategies are being contemplated. Additional investigational drugs that target the production and degradation of the amyloid  $\beta$ -peptide are currently in clinical trials.

### Conclusions

Memory concerns in older women can be caused by self-limited, non-progressive phenomena or disease-related conditions. Depression, anxiety, stress, preoccupation, and loss of confidence can lead women to believe they have memory problems when, in fact, their learning and recall are normal. On the other hand, memory loss due to brain disease leads to more pervasive forgetfulness. Isolated memory loss on a pathological basis, in the setting of preservation of other mental functions, may represent mild cognitive impairment.

Mild cognitive impairment is, in turn, a risk factor for the future development of Alzheimer's disease or other dementing illnesses. Dementia represents the syndrome of progressive

*(continued on page 31)*