

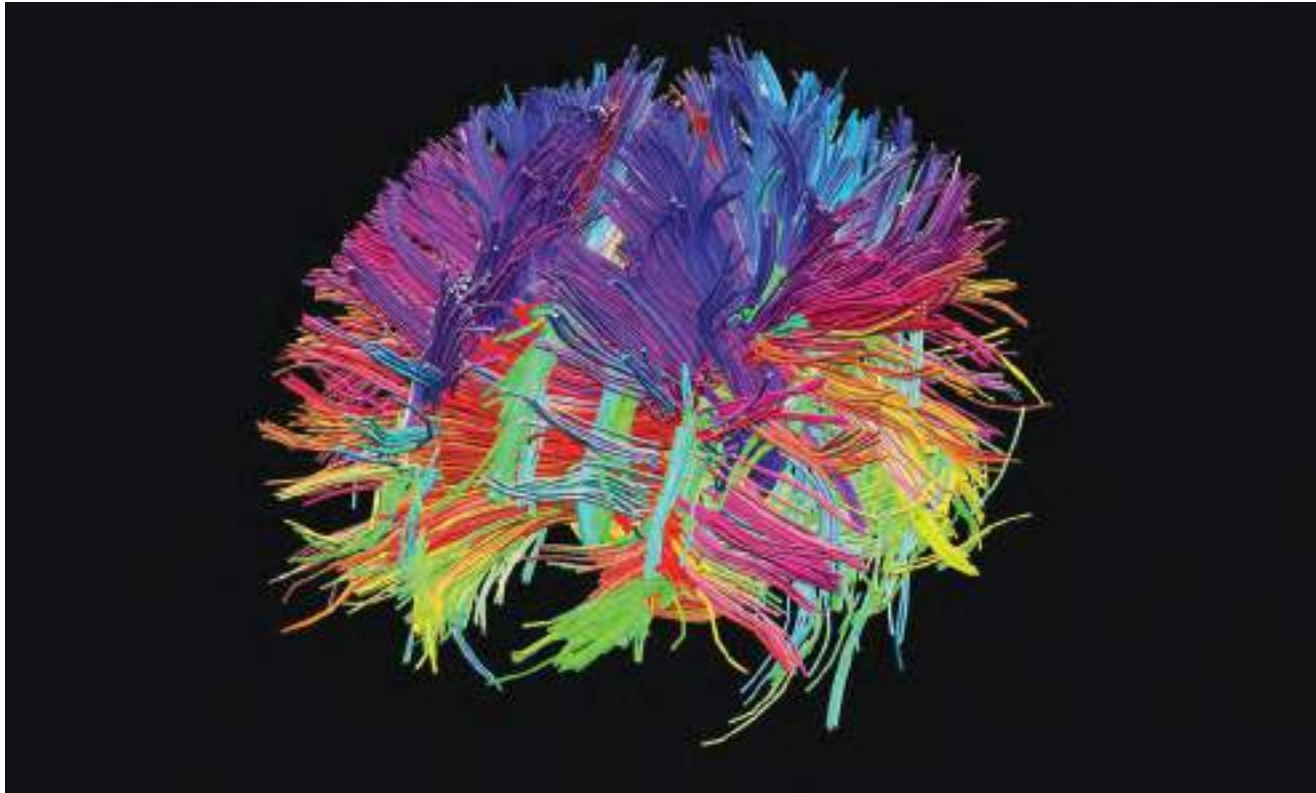
# DIMENSIONS

The Newsletter of the University of Washington Alzheimer's Disease Research Center • SPRING 2013

**MEMORIES MADE AND UNMADE:  
ALZHEIMER'S EFFECTS ON FOUR STAGES OF MEMORY**



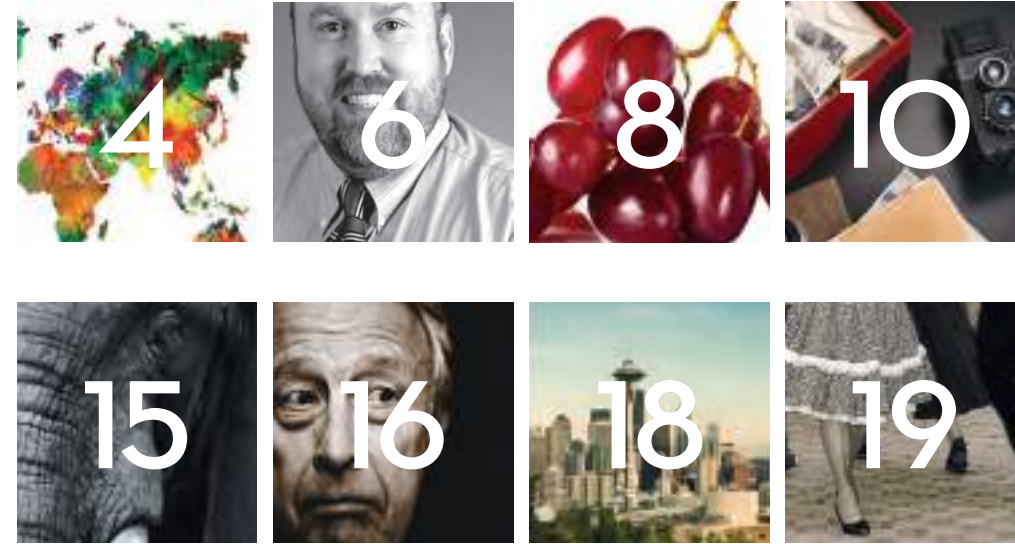
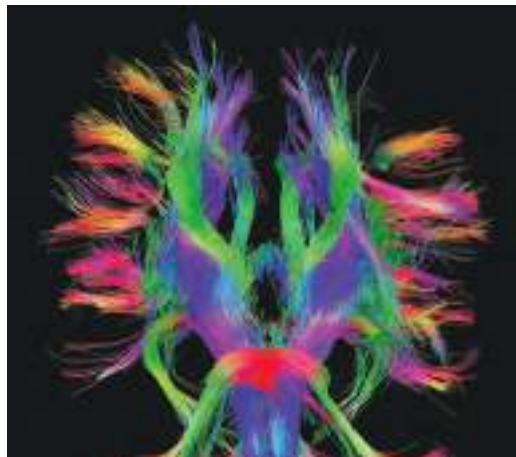
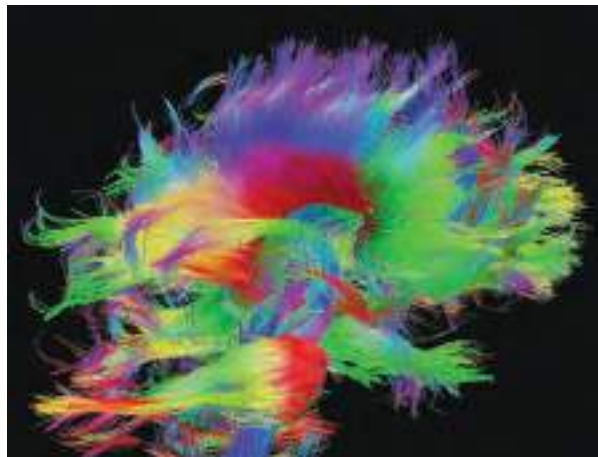
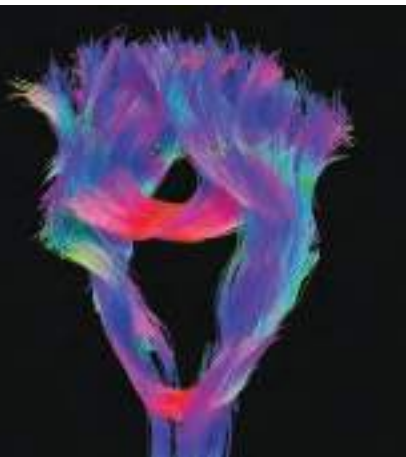
- **Resveratrol: The Red Grape Supplement**
- **Walking the Neuro-Path: An Interview with Our New Director, Dr. Thomas Montine**
- **Anger Management: Caregiver Tips for Handling Alzheimer's Behavioral Symptoms**



Over the years, we have learned a lot about the structure and function of particular areas of the brain, but the secret to understanding neurodegenerative diseases like Alzheimer's may lay in discovering more about the connections between those various areas. New developments in brain imaging now allow researchers to see these connections. **The Human Connectome Project** is a large-scale multi-site project with the ambitious goal of mapping the neuronal connections that underlie human brain function. Researchers at the Human Connectome Project believe that learning more about these connections in healthy human brains will help us understand why diseases like Alzheimer's and Parkinson's develop and affect us in the way that they do.

**About these images:** Recently developed diffusion imaging processes create the bright and highly detailed images shown here. These images depict a 3-D map of the movement of fluid in the brain, with each color corresponding to a particular pattern of fluid movement. When combined with what we already know about the way that fluid moves through different tissues, researchers are able to use these images to predict the connections between different brain areas. •

These images are provided courtesy of the Laboratory of Neuro Imaging at University of California, Los Angeles, and the Martinos Center for Biomedical Imaging at Massachusetts General Hospital, Consortium of the Human Connectome Project.



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**DIMENSIONS**

The University of Washington Alzheimer's Disease Research Center (UW ADRC) is affiliated with the University of Washington and the Veterans Affairs Puget Sound Health Care System. The UW ADRC has been funded by the National Institute on Aging since 1985 to facilitate cutting-edge research on Alzheimer's disease and related dementias. In particular, the UW ADRC focuses on Alzheimer's biomarker research and advancing clinical treatment for dementia. The UW ADRC is also supported by the Friends of Alzheimer's Disease Research, the Alzheimer's Association, and members of the public.

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# GLOBAL RESEARCH UPDATES

The most prominent current hypothesis to explain the development of Alzheimer's disease suggests that the disease may be caused by the formation of toxic beta amyloid protein plaques in the brain. Several treatment trials have investigated newly developed drugs that target the accumulation of these protein plaques, and several treatment trials are planned for the coming year. Here are a few of the most noteworthy.

## Completed Studies

### Solanezumab for the Treatment of Mild-to-Moderate Alzheimer's Disease

This fall Eli Lilly and Company announced disappointing results for their phase-three clinical trial of solanezumab, a drug that targets beta amyloid proteins that many scientists think may play a role in Alzheimer's disease. The eighteen-month study of more than 2,050 participants with mild-to-moderate Alzheimer's disease found that the drug showed no benefit in preventing the progression of Alzheimer's. However, there may be a silver lining to this disappointing news. After further analysis, researchers found that though the drug did not show a positive effect in the study population as a whole, there may be evidence to suggest that it modestly slowed cognitive decline for study participants who were in the earlier stages of Alzheimer's.

### Bapineuzumab in Patients with Mild-to-Moderate Alzheimer's

More disappointing news came from Janssen (a subsidiary of Johnson & Johnson), Elan, and Pfizer this fall when they halted four eighteen-month, phase-three studies of bapineuzumab, a drug that targets beta amyloid plaques in the brain, flagging them for removal by the body's immune system. In these studies, the drug failed to slow cognitive decline in participants with mild-to-moderate Alzheimer's, regardless of whether those participants were genetically predisposed to the disease.

## Future Studies

In response to the results from recent studies, researchers are putting more emphasis on *when* interventions targeting beta amyloid are employed, as these treatments may only be effective in the early stages of the disease when symptoms are not readily apparent. Three preventative studies are due to start in 2013 that will attempt to target Alzheimer's earlier in the disease process.

### Alzheimer's Prevention Initiative (API) Study

The National Institutes of Health, Banner Alzheimer's

Institute, University of Antioquia in Colombia, and Genentech are collaborating on the first large-scale prevention study of Alzheimer's disease in cognitively healthy individuals. This five-year study will evaluate the effectiveness of an experimental anti-amyloid antibody treatment called crenezumab in preventing or delaying the onset of Alzheimer's in people who are at high risk for developing the disease. The study will be conducted in 300 members of a 5,000-person extended family in Colombia. Many of these family members have a rare genetic mutation that typically triggers Alzheimer's symptoms around age forty-five.

### Dominantly Inherited Alzheimer Network (DIAN) Study

This two-year, 240-person study will investigate three drugs—solanezumab, gantenerumab, and a BACE inhibitor—as potential preventative treatments for individuals with a genetic predisposition to develop Alzheimer's. The study is a multi-site collaboration between the National Institute on Aging and Washington University School of Medicine. It will enroll 160 people from the United States, the United Kingdom, and Australia who have genetic mutations that make it almost certain they will develop Alzheimer's at a young age, as well as 80 of their family members who have not inherited the known disease-causing mutations.

### Anti-amyloid Treatment in Asymptomatic Alzheimer's (A4)

This three-year study will enroll 1,000 healthy and cognitively normal seniors who have no genetic predisposition to develop Alzheimer's. Five hundred of the participants will be selected because of evidence that beta amyloid plaque has already built up in their brains. This accumulation of plaque may be an early marker that the Alzheimer's disease process has begun. The trial, which will be run through the Alzheimer's Disease Cooperative Study (ADCS), will test a yet-to-be-named anti-amyloid drug to evaluate whether it can delay the onset and slow the progression of the Alzheimer's disease process. •

Hello readers,

Nephrotic syndrome, cancer, heart disease, suicide—these are just some of the companions that Alzheimer's disease has in the top-ten most frequent causes of death in the United States. However, Alzheimer's is the only one of these horrific causes of death that cannot be prevented, cured, or even slowed. We look forward to a time when Alzheimer's doesn't crack the top ten, when doctors can prescribe an effective and reliable treatment at the first sign of memory loss. In the meantime, the eradication of Alzheimer's seems like a slow progression of baby steps, one small finding after another.

In this issue, we take a look at some of the steps that have been taken over the past year, and we spend some time trying to understand how scientists see cognition and memory. Our amyloid-focused research update (to the left) covers several recent amyloid antibody drug trials and considers the potential silver lining from these underwhelming studies—the baby steps, if you will. We also examine the much-hyped resveratrol, an interesting supplement that was recently chosen for a new multi-site Alzheimer's treatment clinical trial. "Memories Made and Unmade" takes the elusive fabric of memory and attempts to pin it down, considering how our memories are made and stored. In "Anger Management," you can find out about difficult behavioral changes that often accompany the progression of Alzheimer's and then learn some ways to navigate those behavioral changes—we hope this article will be helpful for those of you who are caregivers.

We are always looking for interesting article topics, artwork, and new community opportunities, and we love to hear your feedback. If you have something in mind that you think might be worth featuring, or if you want to share your opinion on the latest issue, please contact Sydney Lewis at [sydney.lewis@va.gov](mailto:sydney.lewis@va.gov).

Happy reading,

Murray Raskind, MD  
Education Core Director



Sydney Lewis  
Dimensions Managing Editor



## Alzheimer's Program Support Fund

The ADRC's Program Support Fund helps junior faculty to use their expertise and innovation to pursue promising research studies within the UW ADRC. Your community partnership in the Program Support Fund is essential to these continued efforts to find better treatments and a prevention for Alzheimer's disease. For more information regarding the Support Fund, please contact Susan Martin at 206.764.2703 or 800.329.8387 x62702. Checks can be made out to "UW ADRC" and mailed to: VAPSHCS, S-116 MIRECC, Attn: Susan Martin, 1660 South Columbian Way, Seattle, WA 98108. To donate online, visit [www.washington.edu/giving/make-a-gift](http://www.washington.edu/giving/make-a-gift) and search for "Alzheimer's Program Support Fund."

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# Walking the Neuro-Path

## An interview with our new director, Dr. Thomas Montine

Last spring Dr. Thomas Montine became the new director of the UW ADRC. Dr. Montine is the head of the UW ADRC Neuropathology and Targeted Molecular Testing Core, as well as chair of the Department of Pathology and professor of neurological surgery at the UW.

### You work as a neuropathologist for the UW ADRC—what does that mean?

A neuropathologist is a laboratory physician who focuses on diseases of the nervous system. For example, when a patient goes into surgery but the doctors haven't yet settled on a firm diagnosis, they'll get a tissue sample from the patient and then call a pathologist. The pathologist will study the sample in the laboratory. It's the pathologist's job to figure out what's wrong with the patient so that an appropriate treatment can be provided.

I do autopsy neuropathology. This means that after a patient who is enrolled in the ADRC's autopsy program passes away, I join other neuropathologists in our neuropathology core in carefully looking at the former patient's brain tissue. We compare our observations of the brain tissue to the medical history that the researchers at the ADRC have collected up to that point. Then, every month or so, we hold a clinical pathological conference where many of the ADRC researchers and pathologists put their heads together and decide how the patient's clinical history relates to what we've found.

### How did you come to work in medicine and Alzheimer's research?

I was going to be an astronomer—when I was an undergrad at Columbia University that's what I was planning on doing with my life. Then, due to an administrative fluke, I had to get a last-minute job, and I found one in a biochemistry laboratory. That experience sparked my interest in the health sciences and set me on a path to becoming a doctor, at first with an eye toward cancer research and later with a focus on neurodegenerative diseases. While I was doing my medical training at Duke University, my grandparents were in the depths of Alzheimer's disease, which they later died from, and so I naturally gravitated toward the study of neurodegenerative diseases. From there I chose the neuropathology side of research, not so much because I enjoy autopsy pathology but because it's the best tool we have to study the molecular mechanisms of the disease.



**I believe that learning more about the ways that Alzheimer's begins will put us in a better position to treat Alzheimer's disease in all people.**

### How long have you worked as a part of the UW ADRC, and what brought you here in the first place?

I moved here ten years ago from the ADRC at the University of Kentucky to work at the University of Washington. At the time, I was particularly interested in joining this ADRC. Not everyone knows this, but the UW ADRC is a very strong research center. It is one of the oldest in the country, and it has an exceptional history of contributing to Alzheimer's research and therapeutic interventions.

### Speaking of Alzheimer's research and therapeutic interventions, what's new in the field of neuropathology and Alzheimer's research?

There have been lots of Alzheimer's-related research developments in the area of neuropathology. **The most important thing that we've learned in the past five to ten years is that Alzheimer's disease often exists alongside other diseases that can produce cognitive impairment, particularly in older individuals.** Therefore, the work that we're doing now is not simply to understand Alzheimer's disease but to understand how it interacts with other pathologies in the brain.

### Why is it important that we have an autopsy protocol and a neuropathology core at our ADRC?

There are two important roles for the autopsy program. The first is a diagnostic role. Dementias are often difficult or impossible to distinguish from one another based only on symptoms. When a person enrolled in our autopsy program passes away, we are able to determine a concrete diagnosis, and we can then give that diagnosis to the family of the loved one who has passed away.

The second is a research role. Animals can be used to study many types of human diseases. However, despite much effort, researchers have yet to succeed in re-creating the characteristics of Alzheimer's disease accurately or reliably enough to study it in any other species. Thus, in order to study Alzheimer's disease, we have no choice but to look at the brains of those people who had the disease. **The use of real human tissue remains the gold standard for Alzheimer's research.**

### Who are we looking to enroll in our autopsy program?

We are looking to enroll anyone who has been involved in our studies or our registry. It doesn't matter to us whether a person has dementia—the tissue samples from both people with dementia and people without dementia are extremely valuable research resources.

We've learned now that the Alzheimer's disease process starts much earlier than the outward symptoms of the disease. This means that it's really important for individuals with normal memory to participate, as they may be in an earlier stage of the disease process where there are not yet any symptoms. Having access to samples from such people gives us a chance to look at what happens in the brain leading up to the onset of dementia.

### What are your goals or research directions for the ADRC over the next few years?

We need to gain a much better understanding of the very early stages of the illness. That kind of an understanding will necessitate a significant shift, not only in *our* research priorities but in the research priorities of other ADRCs as well. We will still look for ways to help people in the more advanced stages of Alzheimer's, but our main focus will shift somewhat to the earlier stages of the disease. **I believe that learning more about the ways that Alzheimer's begins will put us in a better position to treat Alzheimer's disease in all people.** •

For more information on our neuropathology core or our autopsy program, consult our website: [www.uwadrc.org](http://www.uwadrc.org)

# Resveratrol

## THE RED GRAPE SUPPLEMENT

By Lindsey Beach, Andrew David, and Sydney Lewis

If you drive a few hours east from our UW ADRC offices at the Seattle campus of the Veterans Affairs Puget Sound Health Care System, you'll find yourself in what may be a magical land of miracle fruits. In the rain shadow of the Cascades, the Columbia Valley region happens to be the second-largest producer of wine in the United States, and some researchers believe that its crop of red grapes may be a source for the anti-aging elixir known as resveratrol.

Resveratrol is a naturally occurring compound that is found in red grapes, chocolate, peanuts, Japanese knotweed, and some berries. These plants produce resveratrol to help protect them from fungal infections and environmental stressors, such as high levels of UV light. As it turns out, the compound may also have protective benefits for people as well.

For centuries traditional Chinese medicine has used resveratrol as the main active component in a treatment derived from Japanese knotweed. However, resveratrol didn't make its way into the ledgers of modern Western science until the late 1990s. At the time, researchers were attempting to make sense of the "French paradox," that is, the low rate of heart disease found in French populations despite their high consumption of wine and saturated fats. These researchers discovered that

the consumption of moderate amounts of red wine might be responsible for this paradox, perhaps due to its resveratrol content. It is unlikely that resveratrol explains the entirety of the French paradox, but this revelation sparked significant interest among scientists in the resveratrol compound.

Since then, researchers have discovered that resveratrol may have antiaging, neuroprotective, antifungal, antiviral, and anticancer effects as well. The antiaging and neuroprotective possibilities have been particularly interesting to Alzheimer's researchers. At this time, the resveratrol research that has been conducted in humans is still insufficient to claim that it has any definitive benefits for dementia, but the results from animal studies have been promising enough to spur several new trials.

Although various researchers are still exploring resveratrol's possible antiaging effects, the basic mechanisms of the compound have already been roughly outlined. To begin with, compelling evidence suggests that restricting calorie intake improves overall health. Calorie restriction has the potential to improve health by affecting the regulatory pathways of aging-related diseases, such as cancer, diabetes, and Alzheimer's. Based on this understanding, scientists theorize that one of the ways that resveratrol works is by mimicking several of the chemical outcomes of

calorie restriction. More particularly, they believe that resveratrol may directly activate sirtuins, a class of enzymes involved in calorie restriction.

Sirtuins may be particularly helpful in the search for an Alzheimer's treatment due to two specific promising effects of the proteins. In a 2010 study at the Massachusetts Institute of Technology, researchers demonstrated that sirtuins activate a pathway of proteins in mice that stimulate the brain to repair damaged neurons. Given that neuronal damage and neuronal death are the causes of Alzheimer's onset and progression, a dietary supplement like resveratrol that potentially triggers these sirtuins could have beneficial effects for people in all stages of Alzheimer's disease.

The second potential advantage of sirtuins and resveratrol was highlighted in a 2008 study by researchers at Cornell University. After providing mice with a large dose of the sirtuin-activating dietary supplement resveratrol, these mice showed significantly reduced beta-amyloid plaque formation compared to mice that did not receive the resveratrol treatment. It is well established among scientists that beta-amyloid plaques are one of the hallmarks of Alzheimer's and other neurodegenerative diseases, and thus, preventing their formation may be one way of treating Alzheimer's. Researchers hypothesize that dietary supplements of resveratrol may reduce beta-amyloid plaques associated with age-related changes in the human brain as well.

The possibility that resveratrol may have similar effects in humans is currently being explored by a group of Alzheimer's researchers through a clinical trial of resveratrol. The study

is being conducted by the not-for-profit Alzheimer's Disease Cooperative Study at twenty-six university-affiliated sites across the United States, including the UW ADRC. The goal of this phase-II study is to determine the safety, tolerability, and effectiveness of a dietary supplement of resveratrol as a possible treatment for Alzheimer's disease. The impact of resveratrol will be evaluated by examining various protein levels in spinal fluid and other biomarkers that are important to measuring Alzheimer's progression and treatments. In this year-long study, people over the age of fifty with a diagnosis of probable Alzheimer's will be given resveratrol or placebo, an inactive substance that looks like the study drug but contains no active medication. The results of this trial will determine whether daily resveratrol therapy has an effect on the amyloid plaque buildup in the brain and whether it is beneficial in delaying or altering the deterioration of memory and daily functioning in people with Alzheimer's disease.

Given that resveratrol is most famous for its presence in red wine, many people who hear of these research efforts joke that they will skip the clinical trial and simply add another glass of merlot to their dinner menu. Although increasing wine intake is one way of increasing resveratrol consumption (albeit not necessarily a medically advised strategy), the concentrations of resveratrol found in these investigational trials are many times higher than a glass of wine—people would have to drink more than forty-five bottles a day to ingest the same amount of resveratrol that they would absorb in a daily clinical trial dose. Obviously, that level of resveratrol consumption is territory for medical investigators and not sommeliers. •



### Red Grapes

The skin of red grapes is the most well-known natural source of resveratrol; however, moisture, high exposure to UV light, and other growing conditions can dramatically affect the levels of resveratrol in grape skins.



### Japanese Knotweed

Traditionally consumed in tea or as a vegetable comparable to asparagus, this notoriously destructive species has the highest concentration of resveratrol of any edible plant.



### Peanuts

Peanuts are another natural source of resveratrol. Interesting fact: The level of resveratrol in peanuts increases significantly when they are boiled and decreases when they are roasted.



### Cranberries

Although they don't contain as much resveratrol as some grapes, berries from the Vaccinium family, such as cranberries and blueberries, are another significant source of resveratrol.



### Cocoa

Good news for those of us who love chocolate—cocoa powder, baking chocolate, and dark chocolate contain about as much resveratrol per serving as uncooked peanuts.



### Supplements

Resveratrol is now available at your nearest health food or supplement store in pill form. However, these supplements, which are often derived from Japanese knotweed, often have inadequate safety and quality regulations, so actual resveratrol levels vary.



# MEMORIES MADE AND UNMADE

ALZHEIMER'S EFFECTS ON FOUR STAGES OF MEMORY

By Andrew David, Sydney Lewis, Kiernan Werner, and Drew Christie

Alzheimer's affects a person's memories—we all know this by now. But what does that really mean? Does Alzheimer's crash through our brains, flailing itself haphazardly about the corridors of our mind or does it vary its attack, targeting certain kinds of memories with more precision than others? In this article, we walk through the basics of each type of memory, the ways that different kinds of memories work together, and the particular memory changes that can be expected if someone develops Alzheimer's disease.

## Introduction

Our memories form the architecture of who we are. They are the places we've been and the people we've met; they are everything we've learned from our successes and failures, as well as the many skills we've picked up along the way. Memory guides us through day-to-day life, assembling a scaffolding of knowledge and experience so we can write a sentence, make a sandwich, and chat with friends at a party.

Memory also functions as our brain's filtration system. Every minute it records and discards countless feelings and facts, and then it sorts, catalogs, and prioritizes these details, churning our vast compendia of experiences until tangible lessons and concrete thoughts emerge. And from a psychobiological perspective, this brain activity—this collection of processes that help us attain, store, and retrieve life's data sets—is our memory. Scientists do not yet completely understand all of the nuances of memory, but one way to pull together the threads of what we do know is through stage theory, a philosophy of cognitive development that describes memory as a progression of stages which move from sensory memory to working, short-term, and long-term memory.

## Sensory Memory

As we experience life, our brain records physical sensations in real time. The things we see and touch, the things we hear and taste and smell, all the input our bodies receive from their respective sensory organs—a precise snapshot of everything is processed by our sensory memory, a temporary holding place where our mind can make split-second assessments of our surrounding environment. But the life span of these sensory memories is very brief. For example, auditory information—the honk of a horn, the minor chord of our favorite concerto—remains in the sensory memory for only three to four seconds. And visual information generally lasts no longer than half a second.

As we age, our sensory memory systems stay relatively intact. However, some research suggests that if a person develops Alzheimer's, the length of time that sensory memories stick around will shorten as the disease progresses.

Generally, we forget about 60 percent of what we hear, unless, of course, we take some kind of action with the words we hear.

## Working Memory

Working memory is our mental workspace. It functions as the transition point from our fleeting sensory memories to the somewhat more permanent short-term memory. Working memory is the place where we can temporarily deposit information we receive from our senses (such as a sentence we hear spoken in Spanish) while we actively manipulate it using knowledge from our short- and long-term memory (e.g., translating that sentence into English). This working-memory process allows us to perform complex activities like reasoning and comprehension. Unlike sensory memory, which tends to work



on autopilot, subconsciously sifting through our observations of the world around us, working memory consists of information that we are more consciously processing, and it requires our focus and attention to function properly.

The duration of time that we can store information in our working memory can range anywhere from a few seconds to several minutes, depending on our concentration abilities and our interest in that particular information. Our brains are constantly being bombarded with sensory input that competes for space in our working memory, and they will thus discard information they deem less important or less interesting. For example, if you sat down to a game of chess in a day-care center and were attempting to consider the consequences of several potential chess moves, your ability to mentally shut out the noisy toddlers would dictate how much working memory you could dedicate to strategizing.

For individuals with Alzheimer's disease, auditory working memory tends to function at the same level as healthy individuals of their age group until the disease progresses to a moderate stage. However, research has



shown that individuals with Alzheimer's perform significantly worse than their peers on tests examining the visual and spatial working memory, even at the earliest stages of the disease.

**A study at the University of Michigan suggests that working memory performance is directly affected by a person's surroundings and environment. Two groups of individuals were tested on their working memory performance, one group after a relaxed walk in a quiet park and the other group after navigating busy city streets. The individuals who had been walking the city streets scored far lower on the tests.**

### Short-Term Memory

As one might think, short-term memory refers to our capacity to hold a piece of information in our mind for a small amount of time.

Our short-term memory allows us to temporarily keep things in mind that we don't necessarily want to remember forever but that we might want to keep for a few hours or a few days. It might be handy, for instance, to remember who we saw at lunch yesterday, but unless it was a very special occasion or something especially exciting or unusual happened, the guest list at our ordinary afternoon meal probably will not be important enough to remember a year from now; this is a classic example of short-term memory. Our short-term memory temporarily maintains this kind of information in our brain's neural circuits so that it is available if over the next several hours or days we deem that information important enough to keep. In that case, it will then be semipermanently fixed into a longer lasting and more stable memory, either through conscious repetition or because of the memory's emotional significance to us.

Short-term memory is one of the first parts of memory to be affected by Alzheimer's disease. Although many other factors can affect short-term memory, like distraction, depression, stress, and grief, short-term memory loss is used as one of the primary diagnostic features of early-stage Alzheimer's.

**Short-term memory appears to operate phonologically, or according to sounds. For instance, English speakers can typically hold seven digits in their short-term memory, whereas Chinese speakers can typically remember ten digits. This is because the Chinese words that correspond with particular digits are all single syllables, whereas the English words are not always single syllables—for example, in English the digit eleven is three syllables.**

### Long-Term Memory

The final destination for the events and facts that enter into our mind is our long-term memory. You can think of long-term memories as your memory bank; this is where our memories sit silent and idle when we aren't using them. It is where they wait to get activated.

There are two main divisions of long-term memory: declarative memory and procedural memory. The main difference between these two memory divisions is the extent to which conscious control is involved in the recollection process. Declarative memory, which is also called explicit memory, is often thought of as the conscious memory, as it involves the conscious recollection of information. Declarative memory is

also what people most often mean when they speak of memory. We use our explicit memories when we try to recall events, facts, and names, as well as the meanings of words and symbols that we have learned.

Procedural memory differs from declarative memory in that it allows for learning outside of our conscious awareness. Unlike declarative memory, from which we actively and consciously recall information, we pull up implicit memories subconsciously while performing a task. A classic example of procedural memory is learning how to walk or how to ride a bike. If sometime in your life you learned to walk, there is no need to consciously remember how to take a step every time you must get from point A to point B; your body just does it. Given that this type of memory is subconscious and automatic, most people fail to recognize its critical role in routine, daily tasks—such as when we brush our teeth, get dressed in the morning, or sign our names to a pile of government forms.

These two types of long-term memory, declarative and procedural memory, are not equally affected by the neurodegenerative effects of Alzheimer's disease. The formation of new declarative long-term memories from short-term memories depends on a part of the brain called the hippocampus. This structure is responsible for, among other things, turning temporary changes in neuronal structure (i.e., short-term memories) into long-term changes (i.e., long-term memories). The hippocampus is one of the earliest brain structures affected by Alzheimer's disease, and thus it is not surprising that individuals with Alzheimer's easily forget things that they have learned recently. This can seem strangely counterintuitive to caregivers and family members, as declarative memories that have already been formed, especially very old ones like memories from childhood and young adulthood, have a tendency to stick around until the late stages of the disease. Thus, it is not uncommon to hear someone remark that "My dad can't remember what we did on Tuesday, but he can tell me all about what he was up to sixty years ago!"

Procedural memory, however, tends to be one of the best-preserved types of memory for people with Alzheimer's disease. The process by which new procedural memories form does not appear to use the hippocampus at all, and therefore, procedural memory doesn't suffer from damage to that area in the way that declarative memory formation does. Instead, the formation of procedural memories appears to be governed by the cerebellum, putamen, caudate nucleus, and the motor cortex, parts of the brain that are related to motor control. In fact, researchers have found that until the later stages of the disease, people with Alzheimer's or dementia are able to continue improving at a physical task, even when they are unable to remember ever doing the task before.

**The hippocampus, an area of the brain that is essential to the formation of new long-term declarative memories, gets its name from its shape. Hippocampus is derived from the Greek word hippocampus, a combination of hippos and kampos, or horse and sea monster.**

### What Can Be Done?

Although we haven't yet discovered a way to salvage visual and spatial working memory, short-term memory, or long-term declarative memory from the harmful effects of Alzheimer's disease, there are some small things that we can do as we age to help us keep our memories sharp.



**Diet and exercise:** The brain is an organ, just like any other organ, and it is thus affected by how we treat our bodies. If the food that we give our brains is low quality, it is unfair to expect them to perform at a high level. Many research studies have also shown that physical exercise not only helps keep our precious neurons healthy but that it also can help our neurons grow.

**Exercise includes mental exercise:** It would be odd to expect our biceps to stay strong if we never lifted anything.

Likewise, we can't expect our brains to stay strong if we never make them work. There's no reason to do cross-words if you hate them, but it is a good idea to find some kind of a mental challenge to pursue regularly.

**Hang out with friends and family:** Many studies have shown that social activity can help stave off dementia. For people with Alzheimer's, cultivating an active social life can also slow the progression of the disease.

So perhaps we do not have to feel too guilty for skipping the gym, as long as we're headed to a party and not home alone. •

**Our brains are about 2 percent of our total body weight, but they use about 20 percent of our body's energy.**

**How Do Memories Form?**

Each time we have a thought, physical connections are made between the neurons in our brain. A single thought, say a memory of the Beatles song "Eleanor Rigby," is represented by a large grouping of neurons. This means that many years ago, when you first listened to "Eleanor Rigby," a series of "Eleanor Rigby" neurons were activated in your brain. And if you listened to "Eleanor Rigby" with a significant other, say a girlfriend, a series of girlfriend neurons were also activated, and these girlfriend neurons made connections with the "Eleanor Rigby" neurons. This same thing occurs with all sorts of details so that if you were listening to "Eleanor Rigby" in your living room while staring at blue dinosaurs on the wallpaper, the "Eleanor Rigby" and girlfriend neurons would activate and connect to your living room neurons, blue neurons, and dinosaur neurons. And the more you listened to the song, staring at those cute periwinkle pterodactyls while holding hands with your girlfriend, the stronger those connections and their corresponding memories would become—as the old saying goes, neurons that fire together wire together. This effect is so pronounced that the next time you heard the song "Eleanor Rigby," say five years later, the "Eleanor Rigby" neurons would activate and then re-activate roughly the same series of connected neurons. Thus, listening to the layered strings and lonely lyrics of "Eleanor Rigby" might make you think of your girlfriend (who may now be your ex-girlfriend or wife) and your living room. This does not mean, however, that every time you listen to "Eleanor Rigby" the original memory will surface, particularly because each new encounter with the song will add its own layers of memory, such that the next time you hear "Eleanor Rigby," you may think of Alzheimer's research and entirely forget about the blue dinosaurs.

**CURRENTLY ENROLLING UW ADRC RESEARCH STUDIES**

The ADRC is currently enrolling participants in studies aimed at both treatment and prevention. People without memory loss, with mild memory loss, or with Alzheimer's disease may be eligible.

There is no charge or obligation to participate in these studies, and participation is open to all members of the public.

For more information give us a call: **206.764.2069** or **1.800.317.5382** or visit our website : [www.uwadrc.org](http://www.uwadrc.org)



**OH, TO NEVER FORGET**

A prevention for Alzheimer's disease hasn't been discovered, but we are working on it. If you are between the ages of 45 and 64, have healthy cholesterol levels, and do not have memory problems, you may be right for this study!

**Call today**  
**206.764.2069** or  
**800.317.5382**  
[uwadrc.org](http://uwadrc.org)

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*The future of Alzheimer's is in your hands.*

**Volunteers with & without memory concerns are needed for research participation.**

**UW Alzheimer's Disease Research Center**  
**206.764.2069** or **1.800.317.5382**  
[www.uwadrc.org](http://www.uwadrc.org)

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**Confronting the Challenge of Caregiving**

**DIFFICULT BEHAVIORS & ALZHEIMER'S DISEASE**

We are currently studying a generic and inexpensive medication, called prazosin, to evaluate its usefulness in the treatment of difficult behaviors in persons with Alzheimer's disease.

For more information about this study or for other concerns about treating difficult behaviors, please call our center.

**206.764.2069 ∞ 800.317.5382 ∞ [www.uwadrc.org](http://www.uwadrc.org)**

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# ANGER MANAGEMENT

## Caregiver Tips for Handling Alzheimer's Behavioral Symptoms

By Sydney Lewis and Lucy Wang, MD

Caregivers assume an important yet challenging responsibility when they sign on to tend to their sick loved ones, especially when those loved ones happen to have Alzheimer's disease. In addition to the tragic memory loss that we all associate with dementia, many patients with Alzheimer's also experience symptoms of increased agitation and aggressiveness. In response to routine care, these patients may sob uncontrollably, physically lash out at their surroundings, or become verbally upset. Often it isn't even clear what has caused their distress. By learning the medical and environmental factors that trigger such behavior as well as the medications that can alleviate it, caretakers may ease some of the stress of caring for a loved one with Alzheimer's disease.

### Identifying Medical Factors

The first step in understanding what may be troubling a family member is to consider whether any of the following medical conditions may be involved:

**Irritation or pain:** Patients with Alzheimer's disease may be unable to communicate their pain to others and may react to pain with anger or combativeness. Ear, tooth, and urinary tract infections are common causes of irritation and pain that may go unnoticed. Untreated musculoskeletal pain, such as back or arthritis pain, can also contribute to irritability.

**Medication side effects:** The potential side effects from other medications should be evaluated. For example, some antidepressants, such as bupropion (Wellbutrin), and asthma steroids can act as stimulants that increase a person's likelihood of acting aggressively. In addition, the sedating effects of diphenhydramine (Benadryl) may increase confusion and disorienta-

tion in people with dementia; this confusion can exacerbate agitated and aggressive behavior. Therefore, Benadryl should be avoided when it is not necessary for treating allergies.

**Depression:** It is not uncommon for preexisting psychiatric diagnoses such as depression to worsen as a person's dementia progresses. Depression is known to increase a person's irritability, and it may contribute to difficult behaviors.

It is important to talk with a doctor about these concerns—particularly the medication concerns—to determine whether one of these medical factors may be compounding a patient's agitated behavior.

### Identifying Environmental Factors

A situation that seems normal and comfortable to a person without dementia can be overwhelming or confusing to someone with Alzheimer's. Thus, the second step in understanding a

loved one's behavior is to look closely at the environment before, during, and just after a troubling behavior occurs. Some environmental factors to keep in mind include the following: **Time of day:** Do the behaviors occur at the same time every day? Many caregivers have noted that their loved ones suffer from a condition known as *sun downing*, where patients become angrier and less cooperative as evening sets in. The effects of sun downing can be reduced by adjusting a loved one's schedule and then keeping that schedule as regular as possible. Activities with a greater potential for problems, such as a bath or doctor's appointment, can be scheduled in the morning or early afternoon. Medication times can be adjusted so that the patient is not at a low when evening falls. Increased activity and minimized naps during the day may also help encourage rest at night.

**Location:** Do the behaviors often occur in a specific place? Be aware of the lighting, temperature, and noise level in the environment. Changes or extremes in any of these may contribute to changes in behaviors.

It may be helpful to discuss environmental triggers and solutions with a support group or a doctor, nurse, or psychologist who is experienced in geriatric care.

### Addressing Behaviors with Medication

The third step, after examining the medical and environmental context of the patient, is to consider medications. Medications may be most appropriate for loved ones who frequently appear severely distressed, who are disrupting their ongoing health care, and who are at risk of hurting themselves or others. The Food and Drug Administration (FDA) hasn't approved any medications specifically for treating agitation and aggression in Alzheimer's disease, but some of the following medications may be helpful:

**Antipsychotics:** If a person's behaviors are getting in the way of important care or putting caregivers in danger, antipsychotic

medications are often the quickest and most effective way of reducing aggression and agitation. The downside is that these drugs have serious side effects, including an FDA warning that they increase a patient's risk of death.

**Cholinesterase inhibitors:** When general confusion is the main cause of agitation, cholinesterase inhibitors may boost cognition enough to stabilize difficult behaviors. These medications come without the serious side effects of antipsychotics, though they tend to be very expensive and will most likely only be effective for patients who are experiencing less severe symptoms of agitation and aggression.

**Antidepressants:** Current research suggests that when low mood and irritability are the predominant symptoms, some types of antidepressants like citalopram (Celexa) may be helpful.

**Prazosin:** In the 1970s, prazosin was used with marginal success to treat high blood pressure, but the UW ADRC is now investigating how the drug may ease aggression and agitation in dementia. By regulating abnormal levels of adrenaline, ADRC researchers believe the drug may calm disruptive behavior without the sedative effects that are common with other drugs used for agitation.

### Caregiver Health and Resources

Most caregivers eventually experience fatigue from the full-time work of helping their loved ones, and it's very important to manage that stress when it sets in. Otherwise, caretaker stress may provoke additional anxiety in loved ones with Alzheimer's. Adult day health programs, support groups, and respite programs offer caregivers much-needed breaks.

To learn more caregiving tips or to find other important information about caring for someone with Alzheimer's disease, the best resource is the Alzheimer's Association. They have a twenty-four-hour hotline, offer care consultations, and have a broad knowledge of local programs and services. These free services can help caregivers navigate decisions about local adult day health centers, support groups, care facilities, and much more. •

### THINGS TO KEEP IN MIND // DURABLE POWER OF ATTORNEY

A Durable Power of Attorney for Health-Care Decisions is a legal document where you (the grantor) identify someone (the authorized representative) who would have the ability to make health-care decisions for you if you are unable to do so on your own. In some cases this may be a separate document than a Durable Power of Attorney for financial purposes.

#### Who should have one?

Everyone! This is one of those things everyone should make before it's needed.

#### How do I set one up?

There are several ways to set up a Durable Power of Attorney for Health-Care Decisions, including the following:

- Type "how to establish a durable power of attorney for healthcare" into your search engine of choice and follow the instructions. Be sure to choose a form for Washington State (if that's where you live).
- Have your attorney create one for you.
- Contact the Alzheimer's Association at 1.800.272.3900.
- Contact your doctor's clinic; they may have a social worker or patient liaison who may be able to help you.

## NEWS & NEWSWORTHY

On October 23, 2012, several of our UW ADRC researchers, including Murray Raskind, MD; Elaine Peskind, MD; Christopher Gross, MD; Eric Petrie, MD; Kim Hart, PA-C; David Hoff, PA-C; Hollie Holmes; Robert Hanson; Kirsten Rohde, RN; James O'Connell, MSW; and Denise Pritzl, LICSW, received the Department of the Army's Commander's Award for Public Service, for their innovative research and exemplary performance in the treatment and support of Joint Base Lewis-McChord soldiers. This collaborative VA/Department of Defense clinical research team recently completed the first study of any medication for a behavioral problem in active-duty combat soldiers. They demonstrated that a non-sedating medication called prazosin markedly reduced posttraumatic stress disorder symptoms, particularly combat trauma nightmares and sleep disturbance, and thereby improved the soldiers' overall ability to function at work and at home.



## NEW ONLINE RESOURCES

Last fall the UW ADRC launched a brand new website. The new website provides overviews of research participation and procedures, including which studies are currently enrolling, explanations of research projects at the center, and a calendar of upcoming community events.

Do you wonder what exactly cerebrospinal fluid is or how lumbar punctures help ADRC researchers learn more about Alzheimer's biomarkers? The answers to these kinds of questions can be found at the new website. In addition to being a more comprehensive source for information about the ADRC, the visual design and organization of the site have been improved to make it easier to navigate. We hope that the new website is a place where questions can be answered and new opportunities can be discovered.

Visit [www.uwadrc.org](http://www.uwadrc.org) to see the new website. We look forward to hearing your feedback on the improvements. Please send your feedback to [sydney.lewis@va.gov](mailto:sydney.lewis@va.gov)

## COMMUNITY OPPORTUNITIES

### The Alzheimer's Café

*Greenwood Senior Center*  
*Mae's Phinney Ridge Café, 2nd Tuesday of each month*  
 Contact: Carin Mack at 206.297.0875  
<http://www.greenwoodseniorcenter.org>  
 The Alzheimer's Café at the Greenwood Senior Center provides an opportunity for people living with Alzheimer's disease or other dementias and their care partners to socialize in a safe environment with others. No reservations are necessary; the only cost is your dessert and drink.

### Coffee Hour

*1st and 3rd Friday of each month, 10:00 to 11:30 a.m.*  
 For individuals with early-stage memory loss and their friends, family, and care partners. Hosted by the Lakewood Family YMCA in partnership with the Alzheimer's Association. RSVP required: Contact the Alzheimer's Association at 206.363.5500.

### here: now at the Frye Art Museum

*here:now* provides gallery discussion tours and art-making opportunities for those living with dementia and their caregivers to enjoy. The programs are provided free of charge, but space is limited and preregistration is required. Made possible through collaboration between the Frye Art Museum and the Alzheimer's Association. More information available at [http://fryemuseum.org/program/here\\_now/](http://fryemuseum.org/program/here_now/)



HUMAN INTEREST •

# ANNUAL ALZHEIMER'S BENEFIT DANCE

Every February, one hundred or so square dancers gather at the Dance to Remember to raise funds for the Alzheimer's disease research centers of the University of Washington and Rush University. The fund-raising dance was started in 2008 as a way to honor Marty Bahr, a loving father, husband, and brother who was diagnosed with Alzheimer's at age fifty and died of the disease at age fifty-nine.

During Marty's last several years, the Seattle native was an active patient and research participant in Alzheimer's research.



Marty's family started the Dance to Remember to help enable others to receive the same level of quality care and support that Marty received. They also hope to raise awareness about Without Warning, an early-onset Alzheimer's disease support group, and to ensure that Marty's struggle will contribute to the furthering of Alzheimer's research and, someday, to the discovery of a viable treatment.

The dance grows every year and has now raised over \$27,600 for Alzheimer's research. Each year, the Dance to Remember takes place on the last Sunday of February.

As the square dancers do-si-do and promenade about at the Dance to Remember, they may not be thinking of the tangible benefits to their own health, of the ways in which following an allemande left with a right and left grand might keep us sharp. But the brain is like a muscle—it needs exercise to stay in good shape—and that's where dancing can play a role in fighting the onset of Alzheimer's.

If you take a close look at a group of dancers, you'll begin to notice that a relatively high degree of mental complexity is involved in the steps. When people dance, they have to think on their feet; they have to make many split-second decisions as they react to the music, their partners, other dancers, and—in the case of square dancing—shouted instructions from a caller. This requires attention, memory, coordination, and decision making, all of which are major brain activities. On top of that, dance is great exercise for the rest of the body too. It is fantastic for the heart, the lungs, and balance, and it's also a great way to meet new people and spend time with friends and family. •

### MORE INFO

All are welcome to attend the annual dance, whether you are a square dancing pro or a complete beginner. If you are interested in learning more about the Dance to Remember, go to [www.rembertodance.org](http://www.rembertodance.org) or contact Joe Bahr at 206.310.5627.

**\$65,538.87**

total donations made to the UW ADRC from November 2011 to November 2012

112 donations over **\$999**

total number of donations to the UW ADRC **258**

amount raised from the 2012 Dance to Remember **\$5,307**

**57** total number of gifts that were under \$50

**THANK YOU!**

UW ADRC  
VAPSHCS S-116 MIRECC  
1660 S. Columbian Way  
Seattle, WA 98108

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## Make the good old days good again.

Agitated and disruptive behaviors in people with Alzheimer's can make the good times fade and the future seem bleak. The UW ARDC is investigating a drug\* that could reduce these behaviors and brighten the lives of people with Alzheimer's disease and family members.

If you are interested in participating please call 206.764.2069 or 800.317.5382.

Additional information is available at [uwadrc.org](http://uwadrc.org).



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\* Each participant will have a 50:50 chance of being on prazosin or placebo (an inactive substance) for the first twelve weeks of the study.  
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