

## Depression and heart disease: What's the link?

**M**itchell Finkel, MD, a cardiologist at the Clarksburg VA in West Virginia, likes to point out that the word “heart” appears more than 700 times in the Bible, “mostly in the context of your emotions.”

Indeed, people over the ages have viewed the heart as the seat of the emotions. The link is entrenched in our language: Those who are grieving have a “broken heart.” The “heart sings” in those who are happy. Is the connection merely figurative, poetic? Or is there a biological basis for the metaphor?

Researchers have found, in study after study over decades, an undeniable link between emotional illness—namely depression—and heart disease. Not only is depression common among those with heart disease—in fact, it puts patients at greater risk for dying—but it also appears to play a role in causing heart disease in the first place.

“There are some studies going back 50 years demonstrating that depression leads to heart disease,” notes Jeffrey Scherrer, PhD, a psychiatry researcher at the St. Louis VA and Washington University. He was lead author on a recent study of more than 1,200 male twins who served in the military during the Vietnam era. Men who reported depression when they were surveyed in 1992 were twice as likely to develop heart disease in the ensuing years. Even among twins, who share similar or identical genetic vulnerabilities to disease, only those who experienced depression were at greater cardiovascular risk.

But how exactly does depression increase heart risk? One school of thought is that depression is a marker for certain behaviors that harm the body, including the cardiovascular system. Smoking, physical

inactivity, poor diet and non-compliance with medical treatment are known to bring on or worsen many ailments, ranging from heart disease to the common cold. But there’s also evidence suggesting that the mental state of depression itself, independent of any physically unhealthy behaviors, triggers a cascade of hormonal and other changes in the body that damage the heart or blood vessels. Sorting out all these variables and understanding how they interact is a huge theme in medical research.

### The inactivity factor

Mary Whooley, MD, an internist and epidemiologist at the San Francisco VA, believes behavior is key. Her team of investigators on the “Heart and Soul Study” followed more than 1,000 heart patients for an average of nearly five years. The goal was to tease out which physiological or

behavioral factors were most influential in the pathway from depression to heart disease. Their main finding, reported last fall in the *Journal of the American Medical Association*, was that “the association between depressive symptoms and adverse cardiovascular events was largely explained by behavioral factors, particularly physical inactivity.”

Whooley: “Very often, patients with depression don’t exercise, which makes them feel more depressed, which in turn leads to their exercising even less. It’s a vicious cycle that leads directly to heart disease.”

Finkel, who conducts animal and clinical research at VA and West Virginia University, has a different view. He points to experiments in which rats bred to be more

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**Brokenhearted**—Many studies have shown that depression can lead to heart disease. But researchers are still working to unravel how exactly the two diseases are connected.



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susceptible to emotional stress—he says it’s a close-enough model for depression—are more likely to go into heart failure when they are restrained.

“Here’s an animal model that doesn’t have any behavioral issues but is basically programmed differently,” says Finkel. He doesn’t deny that depression-related lifestyle factors such as smoking or physical inactivity obviously contribute to a higher risk for heart disease. But he asserts that physiological factors that are part of the depression profile—though not necessarily linked to any particular behavior—are just as critical in the equation.

### Cardiac abnormalities part of depression

Researchers have identified several biological changes that occur in people with depression, any of which could reasonably make them more susceptible to heart attacks, stroke, heart failure or other cardiovascular maladies: Their hearts beat faster. They tend to have high blood pressure. Their hearts don’t adjust well when they switch activities—from walking to sitting, for example. They have sticky platelets, which increases the risk of harmful blood clots. They have low levels of omega-3 fatty acids and high levels of the stress hormone cortisol.

Some of these factors may be aggravated by smoking, say, or poor diet. But Finkel and others believe there are still baseline abnormalities in depressed patients, independent of their unhealthy behaviors. He points out that prenatally stressed rats—his depression model—have some of the same biomarkers.



**Heart cells under the microscope**—Dr. Mitchell Finkel of VA and West Virginia University and colleague Dr. Fangping Chen examine heart muscle cells from a rat. The team has identified an enzyme that they believe can be “turned off” to help reverse heart failure.

Figuring out how all the lifestyle and biological factors interact is enough to make a researcher’s head spin. So why bother? Isn’t it enough to simply treat the depression and thereby lower the risk of heart disease, without understanding the exact pathway between the two ailments?

That would make sense, except that treating depression doesn’t always appear to improve cardiac health. “There’s no strong evidence that treating depression will reduce the risk for heart attack,” says Scherrer. This is puzzling to researchers because it seems to mock the well-established notion that depression leads to heart disease. And it makes them even more determined to untangle the factors connecting the two conditions.

Finkel cites a large, federally funded trial that found that while cognitive behavioral

therapy modestly improved depression symptoms in heart patients, it did little to cut their risk of further cardiac incidents. Treatment with the antidepressant drugs known as SSRIs, however, reduced the risk of a second heart attack or death by 42 percent.

SSRIs are known to make the blood less likely to clot, and that could be part of why they appear to exert some cardiovascular benefit. “These drugs, independent of the whole mood effect, seem to counterbalance the tendency toward clotting,” explains Finkel.

However, there are also studies in which even SSRIs failed to cut the heart risk for depressed patients. In fact, in some trials the drugs actually made things worse from a cardiac standpoint. Regarding these studies,

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**Most U.S. hospitals lack electronic medical records**—A team with VA, Harvard and other institutions surveyed nearly 3,000 non-federal hospitals in the U.S. and learned that only 1.5 percent of the facilities have a comprehensive electronic records system available across all major clinical departments. Hospitals were more likely to report having an electronic records system if they were larger institutions, major teaching hospitals, part of a larger hospital system, or located in urban areas. VA is recognized as a pioneer in this area, having implemented its electronic health records system in the late 1990s. (*New England Journal of Medicine*, online March 25, 2009)

**Protein reverses Alzheimer’s in animal models**—Memory loss, brain cell degeneration and cell death were prevented or reversed in animal models of Alzheimer’s disease after treatment with a naturally occurring protein called brain-derived neurotrophic factor (BDNF). A team led by Mark Tuszynski, MD, PhD, of VA and the University of California, San Diego, injected the BDNF gene or protein in a series of cell cultures and animal models. The

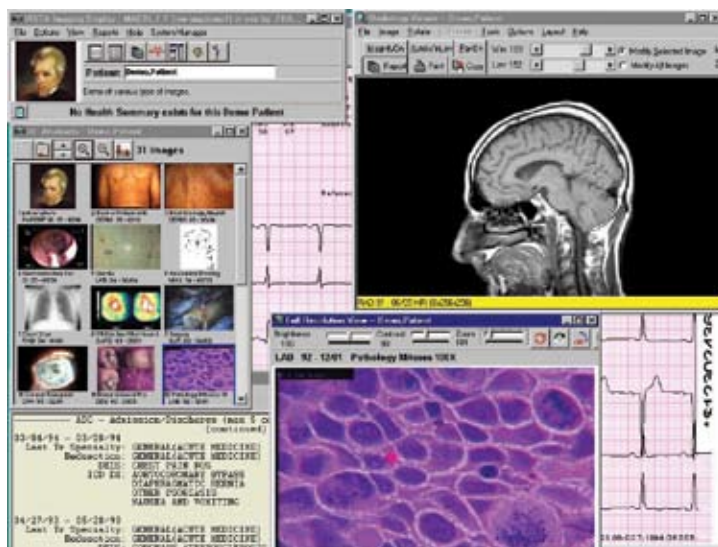


**Drug risk for seniors**—VA researchers and colleagues studied the effects on older adults of multiple prescriptions that act on the central nervous system. See story below.

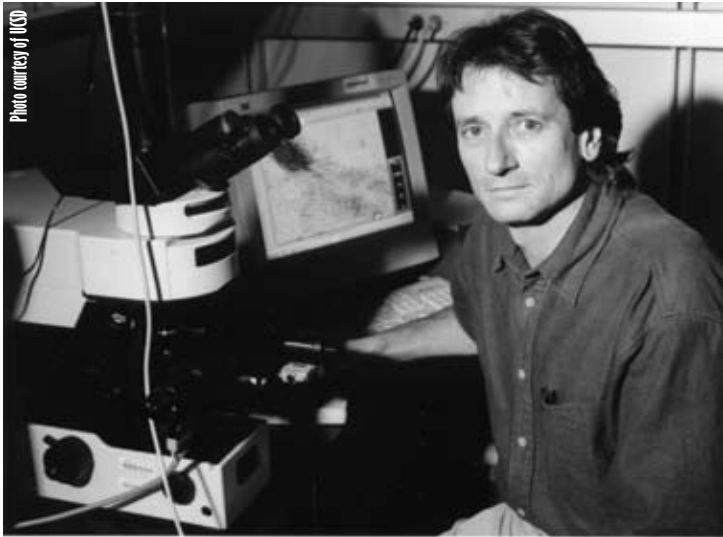
animals included genetically engineered mouse models of Alzheimer’s disease and rats and monkeys that were aged or that had induced damage to a part of the brain that supports memory. In each case, when compared with untreated controls, the animals treated with BDNF performed better on learning and memory tests. And their brains showed restored BDNF gene expression, enhanced cell size, improved cell signaling, and activation in neurons that would otherwise have degenerated. The researchers say the results provide “a rationale for exploring clinical translation to humans.” (*Nature Medicine*, Feb. 8, 2009)

**Elderly at risk from cumulative effects of nervous-system drugs**

—Many older people have multiple prescriptions for drugs that act on the central nervous system, such as painkillers, tranquilizers or antidepressants. But little research has looked at the negative effects from the combined use of these drugs. Two recent studies by investigators with VA, the University of Pittsburgh and other institutions were among the first to examine the impacts on healthy, community-dwelling seniors of multiple or high doses of these drugs. One study found that higher total daily doses of the medications were associated with recurrent falls. The other found that combined use of the drugs, especially at higher doses, may be linked with cognitive decline. The researchers suggest clinicians should use the lowest possible combined doses of these medications, particularly when treating pain and psychiatric illness that occur together. The studies were part of a larger research project called the Health, Aging and Body Composition Study. (*Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, online Feb. 4, 2009; *Journal of the American Geriatrics Society*, February 2009)



**Ahead of the curve**—Electronic medical records like those used in VA—illustrated here by a mock screenshot—are in use at only a small percentage of U.S. hospitals, according to a study by authors from VA, Harvard and other institutions. See story above.



**Seeking Alzheimer’s cure**—A team led by Dr. Mark Tuszynski, of VA and the University of California, San Diego, was able to reverse memory loss in primates by injecting a naturally occurring brain protein. See story on facing page.

**Compound in saffron shows promise for pancreatic cancer**—A team at the Cancer Research Unit at the Kansas City (Mo.) VA, led by Sushanta Banerjee, PhD, conducted a series of experiments to verify the anti-tumor properties of crocetin—a compound derived from the spice saffron that has long been used in traditional medicine against cancer and other diseases. The researchers found that crocetin was effective in thwarting tumor growth both in cell cultures and in mice that had been injected with pancreatic cancer cells. (*Molecular Cancer Therapeutics*, February 2009)



**Grape-derived antioxidant stops lung tumors in lab study**—Lab experiments at the Birmingham (Ala.) VA showed for the first time that proanthocyanidins—an antioxidant compound found in grape seeds, pine bark and other natural sources—could halt the spread of lung cancer in cell cultures and mice. The research, led by Santosh Katiyar, PhD, used mice that had been implanted with human non-small cell lung cancer, the most common form of the disease.

According to the authors, their preclinical findings suggest that proanthocyanidins, which are taken as a dietary supplement by many consumers worldwide, hold promise for lung-cancer prevention and treatment. (*Clinical Cancer Research*, Feb. 1, 2009)



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Whooley notes: “The tough part is to sort out whether it’s just because the people on antidepressants have worse depression. It may be that the worse the depression, the worse the cardiovascular disease. And antidepressant use may just be a marker of worse depression, rather than a mechanism between the depression and the cardiac event.”

Whooley’s “Heart and Soul Study” suggests a different, less invasive angle of intervention: Get people to exercise—a proven remedy for depression and the heart. Says Scherrer, “Exercise is an excellent prescription for all patients, including those with depression.”

## Integrating physical and mental health care

Even though the mechanistic link between depression and cardiovascular disease is still murky, and studies have thus far not conclusively shown that treating depression helps the heart, Scherrer and others say depression should be formally recognized as a major cardiovascular risk factor. He says studies have shown it to be at least as important as diabetes or hypertension in this regard.

The American Heart Association’s website acknowledges that “individual response to stress” may play a role in heart disease but stops short of listing depression as a full-fledged modifiable risk factor.

Nonetheless, many cardiologists are realizing they need to be more aware of depression’s role in heart disease. And conversely, according to Scherrer, psychiatrists should do more cardiovascular screening. “Psychiatrists are fully trained medical doctors,” he says, “but how often do they pull out the stethoscope? Do they ever check blood pressure? Why can’t some basic screening be incorporated into the treatment of psychiatric patients?”

VA may be ahead of most health systems in integrating mental and physical care, notes Scherrer.

Patricia Dubbert, PhD, a psychologist and researcher at the G.V. (Sonny) Montgomery VA Medical Center in Jackson, Miss., agrees. “In our hospital, we try really hard with our mental health patients to make sure they’re in primary care, which would do that type of screening,” says Dubbert. “But it is more difficult to get some mental health patients into primary care, so that’s where I agree with the idea of bringing that type of screening into mental health care. Wherever the patient will go, that’s where we need to provide the care.” Ideally, she says, care should “be integrated in a way that primary care providers have ready access to mental health

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## VA Research Week: May 3 – 9, 2009

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expertise and patients with mental illness have ready access to primary care.”

Part of the answer may lie in collaborative care—an increasingly popular model in VA.

The agency recently funded John Rumsfeld, MD, PhD, of the Denver VA Medical Center, to test a new model of heart-failure care that emphasizes multidisciplinary teams including a primary care doctor, cardiologist and psychiatrist. Managing depression will be integral to the project.

Whether treating depression among the VA patients in the study will ease their heart burden—and reduce their risk of dying—remains to be seen. But even cardiologists are quick to point out that helping patients cope with depression is itself critically important.

Finkel: “We as cardiologists tend to be very focused on whether the depression treatment is going to improve survival. But depression is a horrible disease. You really see this when you take care of depressed patients. It almost makes you cry.” —

### INVESTIGATOR SNAPSHOT



**Memorable prosthetics lesson**—Brian Ruhe, MS, lost both legs in a car crash at age 18. Today, 16 years later, he is a promising biomedical engineer working toward his doctorate at VA’s Chicago Motion Analysis Research Laboratory and Northwestern University. Ruhe also reaches out to others—including Veterans and students—to share his experiences and knowledge. He is seen here talking with eighth-graders at Chicago’s Frances Xavier Warde School about the biomechanics of walking with prostheses.

Ruhe’s research is funded by the National Institute on Disability and Rehabilitation Research. He studies balance in people who have had one leg amputated above the knee. Current models of prosthetic feet do not adjust well to slopes. This can cause balance difficulties and lead to muscle strain and fatigue for users. Ruhe hopes the data he is collecting will help in the development of algorithms to control advanced ankle mechanisms that will allow for improved balance. —