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St. John's Wort and DHEA Found Helpful in Treating Serious Cases of Depression

Two new studies confirm the effectiveness of alternative treatments for depression. In one study, researchers reported that herb St. John's wort was effective in treating severe depression. In the other, the hormone DHEA (dehydroepiandrosterone) improved cases of moderate to severe depression.

The St. John's wort study is particularly significant because the herb has been helpful in mild to moderate depression, but not in severe depression.

Armin Szegedi, MD, of the University of Berlin, Germany, and his colleagues treated 251 men and women with severe depression. The patients were given 900 mg of St. John's wort extract daily or 20 mg of Paxil (paroxetine) daily for six weeks. About half of the patients had their dosages doubled after two weeks because they did not show any initial signs of improvement.

Based on scores from the Hamilton depression scale, a standard test to assess depression, patients taking St. John's wort fared much better than those taking Paxil. Seventy-one percent of those taking the herb improved, and 50 percent of them had a complete remission. In contrast, 60 percent of those taking Paxil improved, and only 35 percent had a remission of depressive symptoms.

Among patients taking St. John's wort, scores on the Hamilton depression scale decreased by an average of almost 57 percent. Scores for patients taking Paxil decreased by 44 percent.

Furthermore, patients taking St. John's wort had about half of the side effects experienced by those taking Paxil. Most of the side effects consisted of dry mouth and an upset stomach.

In the other study, Peter J. Schmidt, MD, of the National Institutes of Health, Rockville, Maryland, used DHEA to treat 46 men and women with mild to moderately severe depression. The subjects ranged from 45 to 65 years of age.

The patients were given either placebos or very high daily dosages of DHEA—90 mg for three weeks and 450 mg daily for another three weeks.

(Note: These are very high dosages that should be taken only under a physician's care.) After six weeks and a one- to two-week "washout" time, the treatments were switched so that all patients took DHEA and placebos at different times for six weeks.

DHEA supplements led to "significant improvement" in the Hamilton depression scale and another test for measuring depression. Twenty-three of the patients taking DHEA had at least a 50 percent reduction in depression scores, compared with only 13 of those taking placebos.

In addition, men and women taking DHEA had significant improvements in sexual function. Improvements were noted in arousal, activity, orgasm, and other aspects of sexuality.

References: Szegedi A, Kohnen R, Dienel A, et al. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomized controlled double blind non-inferiority trial versus paroxetine. *British Medical Journal*, 2005;330:503-507. Schmidt PJ, Daly RC, Bloch M, et al. dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Archives of General Psychiatry*, 2005;62:154-162. □

Perspectives...

Vitamin E Takes Another Hit.

So What's the Real Story?

Vitamin E has taken another media "hit," this time in a study showing an increase in the risk of heart failure. Not surprisingly, most newspaper and television reports failed to note that the same study found a slight reduction in the risk of cancer – or the inherent problems of the study itself.

What's going on here? I'll share a few thoughts.

Medical journals often publish studies of such poor quality that I'm left wondering why editors and publishers waste perfectly good trees. I think this is true of the recent negative vitamin E studies, as well as of thousands of studies on other subjects that do

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not offer any new insights. In this particular case, *Lancet* rejected the vitamin E article a year ago because the editors felt it added nothing new to published research! *The Journal of the American Medical Association* felt otherwise and published the article in its March 16, 2005, issue – with advance and nasty slanting to influence reporters and editors.

A peer review should weed out studies of questionable merit, but it's obvious that peer reviewers do not always take the time to actually evaluate a medical paper before publication. In fact, the "real" peer review appears several months afterwards in the form of letters to the editor, where readers question or attack the study.

Still, you might wonder why any study would even suggest a negative effect from vitamin E. I can offer a couple of reasons.

- Although the increased risk of heart failure in the vitamin E group sounded alarming "statistically," the raw numbers and percentages painted a different picture. Almost the same number of people taking placebos developed heart failure. I was reminded of the book, *How to Lie with Statistics*.

- All of the subjects in the *JAMA* study were seriously ill with either diabetes or advanced heart disease. Half of the patients had suffered heart attacks, and one-fourth had undergone heart surgery. Almost all of the patients were taking several drugs, and there is clear evidence that drug therapy can negate the benefits of vitamin E.

- Complicating the picture, the researchers did not use blood tests to confirm whether or not patients in the vitamin E group actually took the supplements – a problem in some previous studies.

As good as vitamin E is – and the totality of studies justifies its use – it's only one vitamin. No one can reasonably expect any single supplement (or drug) to reverse the consequences of years of dietary and lifestyle abuse.

During the same week, the *New England Journal of Medicine* published three studies confirming that several of the widely advertised and prescribed Cox-2 inhibitor drugs, including Celebrex and Vioxx, increased a person's chances of having a heart attack. And in the same issue, researchers wrote that the gains in longevity over the past century are likely to disappear—mainly because of the increase in obesity.

So what's the real message in all this? It's prevention. It is much more important to stay well than it is to struggle to reverse serious diseases later in life. And we all know the keys to staying well: eating healthy foods, taking supplements, exercising, and managing stress. We just have to make sure we apply what we know every day – before we get seriously ill. —JC

Folic Acid and Vitamin B12 Shown to Reduce Risk of Osteoporosis

Supplements of folic acid and vitamin B12 can significantly reduce the risk of hip and other types of fracture among people who have suffered a stroke, according to a study by Japanese researchers.

After a stroke, the risk of hip fracture increases by two to four times. "Hip fractures are associated with more deaths, disabilities, and medical costs than all other osteoporosis-related fractures combined," wrote Yoshihiro Sato, MD, of the Keio University School of Medicine, Japan.

Sato and his colleagues treated 628 patients, 65 years of age or older, with either a combination of 5 mg (5,000 mcg) of folic acid and 1,500 mcg of vitamin B12 or placebos daily for two years. All of the patients had experienced a stroke at least one year before the study and had residual hemiplegia, or paralysis on one side of the body.

After two years, patients taking the vitamins had a 38 percent decrease in blood homocysteine levels, whereas those taking placebos had a 31 percent increase. Homocysteine is an independent risk factor for heart disease, stroke, and osteoporosis.

According to Sato, a statistical analysis found that patients taking the vitamins had an 80 percent reduction in the risk of fracture. Six of the patients taking vitamins had hip fractures, compared with 27 among those taking placebos. There were eight other types of fractures in the vitamin group, compared with 32 in the placebo group.

Bone density among both groups of patients remained the same throughout the study. That finding prompted Joyce B. J. van Meurs, PhD, and Andre G. Uitterlinden, PhD, to write in an editorial in the *Journal of the American Medical Association* that "bone quality rather than bone quantity explains the difference in fracture risk."

Reference: Sato Y, Honda Y, Iwamoto J, et al. Effect of folate and mecobalamin on hip fractures in patients with stroke. *JAMA*, 2005;293:1082-1088. □

Researchers Report High Incidence of Celiac Disease in Osteoporosis

A relatively high percentage of people with osteoporosis have undiagnosed celiac disease, which likely interferes with their absorption of calcium and vitamin D.

William F. Stenson, MD, of the Washington University School of Medicine, St. Louis, Missouri, evaluated 266 patients with osteoporosis and 574 without the disease. About 20 percent of each group tested positive for IgA or IgG antigliadin antibodies.

However, when these patients underwent

further screening with an intestinal biopsy, nine of those with osteoporosis were confirmed to have celiac disease, compared with only one person in the nonosteoporosis group. These numbers translated to 3.4 percent of the osteoporosis group and 0.2 percent of the nonosteoporosis group.

“The prevalence of celiac disease in osteoporosis is high enough to justify a recommendation for serologic screen of all patients with osteoporosis,” Stenson wrote.

Treating the patients with celiac disease – that is, asking them to follow a gluten-free diet – resulted in improved bone-mineral density after a year. “The improvement in BMD for celiac disease patients on the gluten-free diet was greater than expected for osteoporotic patients receiving standard therapy,” Stenson added.

Avoiding gluten requires patients to avoid all wheat-containing foods and many other grains.

Reference: Stenson WF, Newberry R, Lorenz R, et al. Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. *Archives of Internal Medicine*, 2005;165:393-399. □

Beta-Carotene and Vitamin A Enhance Liver's Detox Enzymes

Many nutrients are known to interact with our genes. Now researchers have reported that beta-carotene and vitamin A activate several genes that help the liver break down drugs and toxins.

Alph Rühl, PhD, of the University of Debrecen, Hungary, and his colleagues studied liver cells that were grown with beta-carotene, vitamin A, or lycopene. They began with the knowledge that some vitamin A and carotenoids derivatives influence gene expression (activation). When activated, genes begin programming the manufacture of specific proteins or enzymes.

Rühl found that beta-carotene and vitamin A, but not lycopene, turned on the pregnane X receptor (PXR), which subsequently activated various genes involved in the liver's detoxification processes. Once activated, PXR increased the activity of CYP3A4, CYP3A7, CYP3A5, all of which help the liver break down “xenobiotics.”

Although alpha-lipoic acid, N-acetylcysteine, and silymarin are better known for their ability to increase detoxification, beta-carotene and vitamin A should enhance liver detoxification of drugs and other toxins.

Reference: Rühl R, Sczech R, Landes N, et al. Carotenoids and their metabolites are naturally occurring activators of genes expression via the pregnane X receptor. *European Journal of Nutrition*, 2004;43:336-343. □

High-Protein, Low-Carb Diet Lowers Blood-Sugar Levels in Diabetics

Switching to a high-protein, low-carbohydrate diet can lead to significant improvements in blood sugar, according to a study of eight men with untreated type 2 diabetes. The diet was designed to contain only 10 percent saturated fat.

Mary C. Gannon, PhD, of the Veterans Administration Medical Center, Minneapolis, Minnesota, asked the eight men to follow a high-protein, low-carb diet for five weeks. After five more weeks, they were switched to a more conventional high-carb, low-protein diet.

The carb:protein:fat ratio in the high-protein diet was 20:30:50. In the more conventional diet, it was 55:15:30.

Overall, the high-protein diet led to a 36 percent reduction of blood-sugar levels over 24 hours, compared with the more conventional diet. In addition, levels of glycated hemoglobin decreased by about 22 percent, from 9.8 to 7.6

By the end of the five-week high-protein diet, the subjects' glycated hemoglobin levels were still declining, and Gannon projected that the final level would be about 5.4 – almost half the level at the start of the study.

She wrote that this type of high-protein, low-carb diet “could be a patient-empowering way to ameliorate hyperglycemia without pharmacological intervention.”

Reference: Gannon MC, Nuttall FQ. Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. *Diabetes*, 2004;53:2375-2382. □

More Evidence on Vitamin D Safety and Its Role in Preventing Falls

There's still more evidence that vitamin D supplements can prevent falls and broken bones in the elderly.

While vitamin D is needed to assimilate calcium for bone, it also plays a key role in maintaining normal muscle strength. In the elderly, weak skeletal muscles make people susceptible to falls, resulting in broken bones.

In a review article in the *British Journal of Medicine*, Geoff Venning, BM, FRCP, notes that a “serious deficiency” of vitamin D is common among elderly housebound people. In some studies, supplements of vitamin D have helped reduce falls, but the findings have not been consistent.

“If vitamin D deficiency is associated with musculoskeletal weakness and falls among elderly

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Quick Reviews of Recent Research

•New anti-inflammatory byproduct identified

Researchers have identified a new anti-inflammatory byproduct of omega-3 fats. The substance, called Resolvin E1 is a very potent anti-inflammatory compound, and it works at least in part by turning off NFkB, a transcription factor that turns on pro-inflammatory genes. The activity of Resolvin E1 is increased when dietary omega-3s are combined with low-dose aspirin.

Arita M, et al. *Journal of Experimental Medicine*, 2005;201:713-722.

• Folic acid problem raises risk of gastric cancer

People with variations in the MTHFR gene, which regulates folic acid activity, are more than two and one-half times higher risk of developing cancer of the gastric cardia, located where the stomach connects with the esophagus. People with a cluster of six genetic variations in the MTHFR gene have more than a six and one-half times greater risk of developing this type of cancer, compared with people who have the normal gene. Supplements of folic acid can

Vitamin D Prevents Falls, Fractures...

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people, why does supplementation with the vitamin sometimes fail to help? The explanation seems to be inadequate dose," Venning wrote. "Two randomized controlled trials have found 400 IU/day of vitamin D to be ineffective in reducing the frequency of fractures..."

Venning pointed out that other studies found that supplements of 800 IU of vitamin D significantly reduce the incidence of falls and fractures.

High-dose supplements of vitamin D have long been discouraged because of a belief about overdose. However, Venning noted that the lowest harmful dose observed was 40,000 IU daily! "A dose of 800 IU daily (or 100,000 IU three times a year) therefore has a 50-fold margin of safety," he wrote.

Other researchers have reported that spending 15-30 minutes in the midday summer sun triggers the body's production of about 10,000 IU of vitamin D.

In his conclusion, Venning wrote, "devotees of anecdote-based medicine who need an example of the dramatic effect of vitamin D on muscle weakness...may wish to note the case report of 'a woman who left her wheelchair' after three weeks of calcitriol [vitamin D] for extremely severe vitamin D deficiency with progressive muscular weakness."

Reference: Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. *BMJ*, 2005;330:524-526. □

offset problems in the MTHFR gene.

Shen HB, et al. *Oncology Reports*, 2005;13:355-360.

• High vitamin E levels lower prostate cancer risk

Researchers compared blood levels of vitamin E in 100 men with prostate cancer and 200 subjects without the disease, all drawn from participants in a larger clinical trial on the use of vitamin E supplements and prostate cancer. Men with the highest blood levels of either alpha-tocopherol or gamma-tocopherol had about half the risk of developing prostate cancer, compared with men who had low blood levels. Other studies have found that vitamin E supplements can reduce the risk of prostate cancer. Gamma tocopherol is found in "mixed tocopherol" vitamin E supplements.

Weinstein SJ, et al. *Journal of the National Cancer Institute*, 2005;97:396-399.

• Pomegranate juice may be good for the heart

Pomegranate juice is rich in antioxidants that may benefit cardiovascular function. In experiments with mice bred for high cholesterol, researchers found that pomegranate juice reduced the development of heart disease. In other experiments with endothelial cells (from the walls of blood vessels), pomegranate juice reduced free radical oxidation and the activity of genes particularly sensitive to oxidation.

de Nigris F, et al. *Proceedings of the National Academy of Sciences*, 2005;102:4896-4901.

• Omega-3 fish oils slow heart rate

In a study of 84 patients, supplements containing 1.5 grams daily of omega-3 fish oils slowed heart rate by an average of 2.1 beats per minute, significantly decreasing the risk of sudden cardiac death. However, the fish oils had no effect of premature ventricular complexes, another risk factor.

Geelen A, et al. *American Journal of Clinical Nutrition*, 2005;81:416-420.

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