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Variety IN the Spice of Life: An Update on the Pleiotropic Therapeutic Potential of Curcumin

By Nancy J. Selfridge, MD, and Santy Daya, PhD

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THE TRADITIONAL CULINARY AND MEDICINAL SPICE TURMERIC (*CURcuma longa*) is sometimes referred to as the "golden spice of life." Native to South and Southeast Asia, this plant is now widely cultivated. The rhizome of the plant is harvested, boiled, dried in a hot oven, and ground to produce a brilliant yellow powder used extensively as a culinary spice in the curries and cooking of India and Asia.[1] In Ayurvedic medicine, turmeric is used as a *dosha* (fundamental constitutional bioenergy necessary for optimum health) balancing agent, a demulcent for cough and respiratory ailments, an antidiarrheal agent, and a treatment for gastrointestinal disorders including helminthic infections. It is also traditionally applied as a poultice or paste to wounds, eye infections, and a variety of skin conditions.[1] Curcumin, a polyphenol, has been isolated and identified as the active ingredient in turmeric. Research interest in curcumin has exploded recently as its pleiotropic mechanisms of action, targeting myriad cellular processes in diverse tissues and cell types, and its complex chemistry have been defined, suggesting multiple possible therapeutic uses. A demand for and interest in natural medicines has further driven this interest.

Anti-inflammatory Effects

Curcumin exhibits in vitro ability to suppress acute and chronic inflammation by inhibiting lipooxygenase (LOX) and cyclooxygenase-2 (COX-2) activities as well as nitric oxide production and reactive oxygen species in macrophages. Production of pro-inflammatory cytokines and other proteins is also curtailed by this agent, as is lipid peroxidation in some tissue preparations. In vivo animal studies affirm curcumin's ability to inhibit inflammation induced by several substances.[2]

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Curcumin's antioxidant and free radical-scavenging functions suggest that it might be useful in the treatment of a wide array of diseases with an inflammatory pathophysiology, including arthritis, COPD, cardiovascular disease, inflammatory skin disorders, and mood disorders. Some clinical potential for curcumin has been shown in patients with inflammatory bowel disease.[3,4]

Chemoprevention Effects

With the worldwide search for anticancer agents, curcumin has rapidly come under intense scrutiny and the results look promising. A review by Hatcher et al, published in March 2008, lists 19 ongoing or not yet open curcumin clinical trials, and eight others in India of indeterminate status.[2] Disease targets in these studies include colon, oral, cervical, gallbladder, and pancreatic cancers, myelodysplasia, and multiple myeloma.

It appears that curcumin inhibits the development of a number of cancers, interfering with multiple steps in the genesis of malignancy. Animal studies have shown that curcumin has a dose-dependent chemopreventive effect in colon, stomach, esophageal, duodenal, and oral cancers and is cytotoxic against bladder tumors in mice. In addition, it appears to have a protective effect against radiation-induced and diethylstilbestrol-stimulated mammary tumors. In other studies, curcumin has a chemosensitizing affect, enhancing activities of antineoplastic agents. This has been demonstrated for cisplatin, the death ligand TRAIL (TNF-related apoptosis-inducing ligand), doxorubicin, tamoxifen, daunorubicin, vincristine, and others. A number of studies have also shown that curcumin has an ability to counteract multidrug resistance in some cancer cell lines. Angiogenesis, an important process in cancer growth and metastasis, is inhibited by this agent.[2]

Summary Points

- Curcumin, the active component in the spice turmeric, is a complex chemical substance that has multitargeting activities in diverse tissues and cell types.
- Curcumin has shown anti-inflammatory, chemotherapeutic, chemopreventive, antimicrobial, neuroprotective, and iron-chelating activities that might have applications in human health and disease.
- More research is needed before curcumin can be recommended therapeutically for any particular disease process. It is probably safe in culinary forms and doses.

Cytoprotective Effects

The ability of curcumin to protect normal cells against radiation injury while radiosensitizing cancer cells, has also been demonstrated, the mechanism remaining unknown.[2] Researchers the world over are trying to unravel curcumin's molecular actions in the hope that it will emerge as a therapeutic tool in cancer prevention and treatment.

For curcumin to exhibit these cytoprotective properties, it would be expected to regulate multiple cell-signaling pathways. This has indeed been demonstrated in studies where curcumin displays activities similar to tumor necrosis factor (TNF)-inhibitor drugs (e.g., Humira®, Remicade®, Enbrel®), vascular endothelial cell growth factor blocker (e.g., Avastin®), human epidermal growth factor receptor blocker (e.g., Erbitux®), and human epidermal growth factor receptor 2 (HER2) blocker (e.g., Herceptin®).[5] It also interferes with control of the cell cycle by several mechanisms related to inhibition of NFκB proteins and induces apoptosis in a number of cancer cell lines, again by several mitochondrial pathways and by suppressing anti-apoptotic proteins.[2]

While interfering with pathways important to tumor cell survival, curcumin also appears to have a cytoprotective effect on non-cancer cells such as increasing activity of glutathione transferases and heme oxygenase, as well as inhibiting procarcinogen enzymes such as cytochrome P45001A.[2]

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Many cytoprotective agents also have metal-scavenging properties and curcumin is no exception. In this respect it has been shown to act as an iron (II) chelator both in vivo and in vitro,[6] thus inhibiting the formation of the dangerous hydroxyl free radical. It is therefore not surprising that it attenuates liver damage induced by iron overdose and even provides hepatoprotection in cholestasis and carbon tetrachloride and ethanol poisoning.[7]

Antimicrobial Effects

Curcumin's multifaceted actions also embrace antimicrobial effects. Researchers at the University of Michigan have shown that curcumin inhibits drug-resistant forms of lethal malaria parasite *Plasmodium. falciparum*[8] and exhibits in vitro activity against *Candida* species and *Paracoccidioides brasiliensis* (the cause of paracoccidioidomycosis).[9] An Iranian study showed that curcumin appears to potentiate the effects of a number of antibiotics. It increases the antibacterial activities of cefixime, cefotaxime, vancomycin, and tetracycline against a test strain of *Staphylococcus aureus*.[10] Apoptosis has been shown to be induced in HPV-infected cervical cancer cells exposed to curcumin.[11-13] A 2004 study in India showed that in HIV-infected cells exposed to curcumin, replication of the virus is halted. The authors hypothesize that this is due to curcumin's inhibition of normal activities of the P300 enzyme in controlling human genes, a mechanism that must remain intact for HIV to replicate.[14] A Cochrane review, though, showed no therapeutic benefit or reduction in HIV viral load or CD4 counts in humans taking curcumin supplements.[15] A 2008 study from Michigan State University showed that herpes simplex virus-1 replication is inhibited by curcumin, but independent of its effects on P300.[16]

Neuroprotective Effects

With the world's population living longer, neurodegenerative disorders have become more prevalent and the search for neuroprotective agents has become an imperative. Here too, curcumin shows great potential to curtail these disorders as it has potent antioxidant and free radical scavenger properties in neuronal tissues. A 2004 study in mice suggests that curcumin might inhibit beta amyloid accumulation in the brain, a pathophysiologic hallmark of Alzheimer's disease in humans.[17] Curcumin has also been shown to be a selective MAO inhibitor, implying that this agent might have antidepressant and neuroprotective effects.[18] Several studies have shown that curcumin has a positive effect on neurogenesis in the hippocampus,[19-21] and since neurodegeneration is associated with stress, depression, and anxiety, the role of curcumin in these disorders should be explored. It is well known that the incidence of Alzheimer's disease in India is very low, but a link to curcumin would need to be established by well-designed epidemiological studies.

Bioavailability

Despite many animal studies demonstrating curcumin's biological effects, it has very limited bioavailability beyond the GI tract, including the liver. When taken alone, oral doses of 2-12 g result in low to undetectable serum levels.[2] Research into altered forms of curcumin that might increase bioavailability is ongoing. Further, it is unclear if heat or oil solubilized forms are better absorbed or if combination with other natural substances and spices, as occurs in the culinary uses of turmeric, may increase absorption and bioavailability. Whether its metabolites might be active and more bioavailable needs urgent investigation.

Safety

Thus far, curcumin appears to have a favorable safety profile, especially in culinary doses. However, some of curcumin's biologic effects deserve consideration. Because curcumin causes gallbladder contraction, patients with known gallstones should be advised to avoid using supplements containing curcumin. Curcumin may increase stomach acid, and thus may be problematic for patients taking stomach acid-reducing medications. Curcumin has shown a blood sugar-lowering effect and might put diabetics on medication at risk for hypoglycemia. These patients should be warned and carefully monitored. It also inhibits platelet aggregation; bleeding problems may be precipitated in patients with known bleeding disorders and those on anticoagulation therapy or other platelet inhibitors such as NSAIDs or clopidogrel (Plavix®). Thus, all patients using curcumin should stop taking these supplements 2 weeks before any scheduled invasive procedure. One study reported lung tumor promotion by curcumin.[22] Patients allergic to turmeric, suffering from or at risk for iron deficiency or on anticoagulation therapy, should not use curcumin supplementation. The same applies to patients with lung cancer or at substantial risk of lung cancer, and patients who are pregnant or breastfeeding. For all others, supplements up to 12 g or 200 mg/kg of body weight daily are probably safe, but research has not clearly indicated a favorable risk/benefit ratio. Though some data suggest that GI upset and diarrhea may result from higher doses, limited clinical trials of the 12 g/d dose have demonstrated only mild nausea or diarrhea and no dose-limiting toxicities.[2]

Recommendation

It is widely agreed by researchers and reviewers alike that more research is needed before recommendations can be made concerning the safe use of curcumin as a therapeutic or chemopreventive intervention for any specific disease. Certainly, if one finds pleasure in consumption of curries or adding turmeric spice in food preparations, this behavior can be encouraged and endorsed and may have some yet unproven health-promoting potential. Considering the multitargeting nature of turmeric and its enigmatic active ingredient, curcumin, in biological life processes, it could prove to be part of the elusive "elixir of life." ❖

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Acupuncture for Depression in Pregnancy

ABSTRACT & COMMENTARY

By Judith L. Balk, MD

Dr. Balk is Associate Professor, Magee-Women's Hospital, University of Pittsburgh; she reports no financial relationship to this field of study.

Synopsis: *Although depression is a serious condition that needs to be treated, many women are reluctant to take antidepressant medications during pregnancy. Depression during pregnancy tends to be underdiagnosed and undertreated. This study aims to evaluate the efficacy of acupuncture for depression during pregnancy, using a three-arm randomized trial. The three arms are acupuncture specific for depression, acupuncture not specific for depression, and massage. Treatment expectation was assessed for both subjects and practitioners. The treating acupuncturists were blind to assignment group, with the individualized acupuncture protocols being assigned to them by more senior acupuncturists. Acupuncture specific to depression significantly decreased depression severity, and it had a significantly greater response rate compared to the control groups.*

Source: Manber R, et al. Acupuncture for depression during pregnancy: A randomized controlled trial. *Obstet Gynecol* 2010;115:511-520.

To assess the efficacy of acupuncture to treat depression in pregnant women, these researchers randomized 151 pregnant women who met criteria for major depressive disorder to receive either the active treatment (acupuncture specific for depression) or one of two control interventions (acupuncture not specific for depression, or massage). Subjects received a total of 12 sessions over 8 weeks. Senior acupuncturists evaluated the subjects and created treatment plans, and junior acupuncturists carried out the treatment plans without knowledge of group assignment. The primary outcome variable was the Hamilton Rating Scale for Depression (HRSD), administered by study staff masked to treatment group. Subjects who received acupuncture specific for depression had a greater rate of decrease in symptom severity ($P < 0.05$) compared to the other two groups. They also had a significantly greater response rate (63%) compared to the control groups combined as one group (44.3%) and to the acupuncture control group alone (37.5%). The control groups did not differ significantly from each other. The acupuncture protocol studied appears to be on par with standard depression treatments with respect to symptom reduction and response rate. Acupuncture could be a viable treatment option for depression during pregnancy.

■ COMMENTARY

Acupuncture is thought to be helpful in treating depression in nonpregnant subjects.[1] Basic science research may indicate the mechanisms involved. Neurotransmitters are thought to play a role in depression.[2] Many antidepressants affect the monoamine systems, such as the serotonergic and norepinephrine (NE) systems. The goal of treatment with antidepressant agents is to correct abnormalities in the serotonergic and NE systems, although it is likely the therapeutic action is mediated by postreceptor intracellular targets. Physiological methods of activating the endogenous monoamine system in the CNS could potentially treat depression.[3] Acupuncture is one method of accelerating the synthesis and release of serotonin and NE in the CNS. Acupuncture also releases opioid peptides and gamma-aminobutyric acid, both of which may be related to depression and mania.[3] Medications, such as selective serotonin reuptake inhibitors and selective norepinephrine uptake inhibitors, improve depression via modulation of neurotransmitters.

During pregnancy, the use of antidepressant medications is controversial. Recently, the American Psychiatric Association in combination with the American College of Obstetricians and Gynecologists reviewed the management of depression during pregnancy.[4] The report noted that both depressive symptoms and antidepressant exposure are associated with fetal growth changes and shorter gestations. Because most studies evaluating antidepressant risks did not control for the possible effects of the depression, it is difficult to definitively assign the effects from the antidepressant medications vs. the effects of depression. Symptoms such as neonatal irritability and neurobehavioral changes are linked with both maternal depression and antidepressant treatment. Some fetal malformations are associated with first trimester antidepressant exposure, although clear patterns do not exist. Late gestational use of selective serotonin reuptake inhibitor antidepressants is associated with transitory neonatal signs known as "poor neonatal adaptation," such as tachypnea and hypoglycemia, and a low risk for persistent pulmonary hypertension in the newborn. Thus, due to the concerns regarding both depressive symptomatology and antidepressant medications, effective alternatives to medications for use in pregnancy would be beneficial.

Human studies suggest that acupuncture is beneficial for the treatment of depression. However, randomized, prospective, controlled trials of acupuncture for depression are rare. One RCT evaluated electroacupuncture vs. amitriptyline in 241 patients with "depressive psychosis." To be included, patients needed scores ≥ 20 on the HRSD. The acupuncture group received a placebo capsule and acupuncture daily for 60 minutes per day. The amitriptyline group received daily amitriptyline, with an average dose of 161 mg per day. Both

groups significantly lowered their HRSD from baseline; no differences occurred between the groups. The authors suggested that the effectiveness of the two modalities is similar.

Inpatient depression was studied by Luo et al.[5] In a randomized, double-blind, placebo-controlled study in 29 inpatients, patients received either electroacupuncture + placebo, amitriptyline, or electroacupuncture + amitriptyline for 6 weeks. Therapeutic efficacy and side effects were evaluated. Based on the results of this small study demonstrating that electroacupuncture was equally efficacious as amitriptyline, a larger, multicenter study was then conducted by the same authors. Patients were randomized to one of two groups: electroacupuncture + placebo or amitriptyline. No difference existed between groups for therapeutic efficacy overall. However, acupuncture was more effective for anxiety somatization and cognitive process disturbance of depressed patients. Side effects of acupuncture were significantly less than that of amitriptyline. Although this study is controlled, a placebo effect for acupuncture still might exist.

Findings from the Current Study

This study enrolled 150 pregnant women who met DSM-IV criteria for major depressive disorder. Women were randomized to receive either acupuncture specific for depression, acupuncture not specific for depression, or massage. The interventions occurred twice weekly for 4 weeks, followed by weekly sessions for 4 weeks. The control groups were comprised of the acupuncture not specific for depression and the massage interventions. The primary analysis was an intention-to-treat analysis of all 150 randomized subjects. Those in the group receiving acupuncture specific for depression experienced a significantly greater reduction in HRSD scores than the participants in the combined control groups. Response rates were significantly higher for the group receiving acupuncture specific for depression than for the combined control groups. The control groups did not differ from each other in their effects. Remission rates were not significantly different between the groups. Expectation of the participants and acupuncturists was also measured. The participants' expectation did not differ between the two acupuncture groups, but the acupuncturists' expectations were lower for the group receiving acupuncture not specific for depression compared to acupuncture specific for depression. This lower expectation was taken into account via statistical analysis, and the difference in provider expectation did not account for the improved efficacy in the true treatment group. Ten unexpected/adverse events occurred, including premature delivery, pregnancy loss, congenital defects, and hospitalization for various causes. All events were considered to be unrelated to treatment. Side effects were minor, and included transient discomfort and bleeding at the needle site.

This study has a few limitations and many strengths. One is the lack of generalizability given the healthy, educated, and predominantly Caucasian population. The approach used, where the treating acupuncturist did not do the assessment, is not what is done in standard care; however, most acupuncture studies do not mimic usual care.

Although the treating acupuncturist did not do the assessment, this study mimics usual care in that the acupuncture treatments were individualized, rather than formulaic, a study strength. The use of two control groups helps to delineate whether effects are from the acupuncture relative to massage, and from the true acupuncture relative to acupuncture not specific for depression. This study had a low dropout rate, and it did not differ by treatment group. The careful assessment of expectation among subjects and providers is also a strength, as it points to whether expectation of positive outcome plays a role in the effectiveness of the outcome.

Although acupuncture was not directly compared to a medication control group, the response rates seen from acupuncture specific for depression are similar to the rates from standard antidepressant medication trials. Importantly, there were not adverse events due to the acupuncture, and side effects were minor. While more research is necessary to make a definitive statement, this study suggests that an individualized acupuncture protocol specific for depression in a healthy pregnant woman could be a viable treatment option. ❖

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Exercise Programs Help Reduce Anxiety in Patients with Chronic Illnesses

ABSTRACT & COMMENTARY

By Dónal P. O'Mathúna, PhD

Dr. O'Mathúna is Senior Lecturer in Ethics, Decision-Making & Evidence, School of Nursing, Dublin City University, Ireland; he reports no financial relationship to this field of study.

Synopsis: *A meta-analysis of 40 randomized controlled trials found evidence of reduced anxiety among patients with chronic illnesses who exercised regularly. The impact of several study variables was investigated as potential contributors to the variability found in different studies.*

Source: Herring MP, et al. The effect of exercise training on anxiety symptoms among patients: A systematic review. *Arch Intern Med* 2010;170:321-331.

A SYSTEMATIC REVIEW WAS CONDUCTED BY SEARCHING the Physical Activity Guidelines for Americans Scientific Database from January 1995 to August 2007. This search was supplemented by further searches of MEDLINE, Web of Science, PsycINFO, and Google Scholar up to the end of 2008. One goal of the systematic review was to provide an overall effect size for patients with chronic illnesses. The second goal was to examine several variables including the type or dose of exercise training and whether these accounted for some of the variation found in the results.

The inclusion criteria for studies were: 1) written in English, 2) participants were sedentary adults with a chronic illness, 3) random assignment to either an exercise intervention lasting at least 3 weeks or an intervention lacking exercise, and 4) an anxiety outcome that was measured pre- and post-exercise training. The search identified 135 potential studies, of which 40 met all inclusion criteria.

The most common conditions among the patients in the included studies were cardiovascular disease, fibromyalgia, multiple sclerosis, psychological conditions, or cancer. The exercise training programs averaged 3 days per week, 42 minutes per session, and lasted 16 weeks. For all outcomes, an effect size was calculated based on standard statistical methods and gave positive values for reductions in anxiety.

A total of 75 different effects were derived from the 40 studies and these were included in the meta-analysis. A random effects model was used for the meta-analysis to take account of heterogeneity among the studies. The overall mean effect size was 0.29 with a 95% confidence interval (CI) of 0.23-0.36. Since the CI did not include 0, the result was statistically significant.

To address the second goal of the systematic review, regression analysis was conducted on six primary moderators: exercise session duration, program length, time frame of anxiety report, fitness level change, intervention type, and comparison type. The first three items were found to be independently related to effect size. Exercise sessions lasting longer than 30 minutes had larger effects than those lasting 10-30 minutes. Exercise programs of 3-12 weeks resulted in significantly larger reductions in anxiety than those lasting more than 12 weeks. The effect size was smaller when anxiety levels were reported for "right now" or during the past week, compared to those measuring anxiety over periods exceeding the previous week.

Several secondary moderators were examined to provide descriptive data about plausible influences on outcomes. Only two were discussed in detail: illness type and adherence. Exercise significantly impacted anxiety levels in those with all types of illness except multiple sclerosis. Adherence was not found to moderate the anxiety outcomes, but this may have been because adherence data were not collected in many studies.

■ COMMENTARY

Anxiety often accompanies chronic illness. However, health care professionals may not recognize symptoms of anxiety or provide suggestions for the relief of anxiety. Failure to address anxiety can negatively impact treatment outcomes and increase the suffering of patients with chronic illness. Pharmacological and cognitive behavioral therapies for anxiety are available, but interest in complementary interventions is common. Such interventions include a variety of relaxation programs. Exercise training may also help reduce anxiety and provide a number of other health benefits.

This systematic review provides clear evidence of the beneficial effects of exercise for those with chronic illnesses (overall mean effect size = 0.29). What is more difficult to interpret is how much benefit these programs are likely to provide. The "effect size" is one way of representing the difference between the mean of the treatment group and that of the control group.[1] It is commonly used in meta-analyses when a variety of methods are used to measure the same outcome. An effect size is sometimes viewed as small if its value is 0.20 or less,

high if 0.80 or greater, and medium if in between.

A meta-analysis provides a summary statistic for outcomes tested in several trials. One of the challenges with having several trials addressing the same outcome is how to account for varying estimates of effects. This meta-analysis found fairly consistent results in that 66 of the 75 effects calculated for the trials were greater than zero. Meta-analysis provides further opportunities to investigate such variability and generate hypotheses.[2] These calculations do not demonstrate causation, but can provide suggestions about factors that can guide future research and make suggestions about factors that are important for clinical developments.

Based on these results, exercise programs had better outcomes when they involved individual sessions lasting longer than 30 minutes. Programs of 3-12 weeks duration had better outcomes, but the reasons for this are unclear. The reviewers speculated that it might be connected to adherence. However, about one-third of the studies did not report information on adherence, which would be important for future studies to record. The time frame over which participants were asked to evaluate their anxiety was also correlated to effect size. Eighty percent of the studies asked about anxiety over the previous week, while anxiety measured over a longer time frame showed greater reductions. The reviewers suggested that researchers should ask about longer-term anxiety levels as this could confirm if exercise has longer-lasting effects. Other nonsignificant findings were also interesting. For example, little difference in effect size was found for age, gender, or whether exercise guidelines met contemporary intensity recommendations.

This meta-analysis was carefully designed and conducted according to the QUOROM statement.[3] These guidelines are intended to improve the quality of reports of meta-analyses, just as the CONSORT statement is designed to improve the quality of RCT reports. The meta-analysis provides clear evidence for the recommendation of exercise programs for those with many chronic illnesses. However, further research is needed before many of the details of such programs can be reliably translated into clinical guidelines. ❖

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Good Only When It's Bad: Drugs for Depression

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *This unique meta-analysis of antidepressant drug therapy for depression focused on randomized, placebo-controlled trials of at least 6 weeks' duration and included subjects with a wide range of symptomatology, from mild to very severe. Subjects with extremely severe depression responded to antidepressant medication better than to placebo, but in all other groups drug therapy was ineffective. Of note, the studies evaluated used only two different antidepressant medications, but the results suggest a gross overreliance on antidepressant medication where it may not be indicated.*

Source: Fournier JC, et al. Antidepressant drug effects and depression severity. *JAMA* 2010;303:47-53.

THE AUTHORS OF THIS PATIENT-LEVEL META-ANALYSIS (or mega-analysis) identified English-language articles of randomized, placebo-controlled trials of FDA-approved antidepressants in the treatment of the full range of patients with major or minor depressive disorder. The intervention had to be of at least 6 weeks' duration, and Hamilton Rating Scale for Depression (HRSD) scores had to be determined at the beginning and end of the intervention phase. The analysis focused on data from six large-scale randomized, placebo-controlled trials that included patients with a broad range of baseline symptom severity, even those with minor depressive disorder (only one of the six studies). The HRSD defines mild depression as a score of 8-13, moderate depression as 14-18, severe depression as 19-22, and very severe depression as ≥ 23. Subjects in the six trials identified had HRSD scores of 10-39.

The tricyclic antidepressant imipramine was used in three trials, while the selective serotonin reuptake inhibitor paroxetine was used in the other three studies. A total of 434 subjects received medication while 284 were given placebo.

The sample was divided into three groups based on

HRSD scores: mild to moderate, HRSD score ≤ 18 (n = 180); severe, HRSD score of 19-22 (n = 255); and very severe, HRSD score ≥ 23 (n = 283). Effect sizes for patients in both the mild-to-moderate (d = 0.11) and severe (d = 0.17) score ranges were below the standard description of a small effect (d = 0.20). For patients in the very severe group, the effect size was significantly greater (d = 0.47). The cutoff for a Cohen d medium effect, however, is d = 0.50.

The authors concluded that the efficacy of antidepressant medication varies as a function of depressive symptom severity. True drug effects were essentially absent in patients with mild, moderate, and even severe symptoms, whereas they were significant for people with very severe symptoms. Only for those people with the highest levels of baseline depression severity were the effects of antidepressant medication markedly superior to placebo.

■ COMMENTARY

One of the perks of being editor of this newsletter is the opportunity to choose the specific articles to be reviewed each month. In this instance, the current article was chosen not only because of its importance and clinical relevance, but for a personal professional reason as well. First to the clinical relevance.

Depression remains a societal plague for which antidepressant medication has long been considered the standard medical intervention. While innumerable studies have shown antidepressant medication to be superior to placebo in the treatment of depression, they focused mainly on people with severe symptomatology. The findings ascribed to those with severe depression seem to have been extrapolated to apply equally well to people with milder disease, such that efficacy was shown, but since the majority of patients seen in clinical practice have significantly milder disease, effectiveness was simply assumed. The results of this trial suggest that a high level of depressive symptomatology is required for a significant response to antidepressant medication. Keep in mind, however, that of the myriad drugs available for the treatment of depression, the studies reviewed here focused on only two, both of them older agents that have been largely supplanted by potentially more effective pharmaceuticals.

As practitioners, some of us have been guilty of a knee-jerk response to a patient's clinical depression. The data suggested, so we thought, that medication could help and so a prescription for the antidepressant of choice (and there were many to choose from) was likely offered, and perhaps some patients benefitted. Other practitioners bucked the trend and stubbornly contended that antidepressants not only didn't help most of their patients, but introduced significant side effects. Both groups were right to some extent.

This editor has been assailed by proponents of both sides of the argument. Some said my prescription pad didn't come out often enough to help, others that I shouldn't have had any confidence in antidepressants in the first place. The results of this study support what has long been suspected and acted upon by many practitioners, including myself — that most people with mild-to-moderate and even severe depression can do well with interventions other than drug therapy, such as cognitive behavioral therapy, acupuncture *(see page 41),* regular exercise, and optimized sleep, among many others. Those who seem to lack the energy to initiate such changes or whose symptomatology is very severe (not discussing the actively suicidal patient), however, might benefit from a trial of low-dose antidepressant medication to help them get moving in the right direction, with the hope of discontinuing drug therapy within 3-9 months.

I claim no specific expertise in the treatment of depression that exceeds that of any of the readers of *Alternative Medicine Alert*. I take this opportunity to share the results of a trial whose conclusions are clinically important, and that also support a stance I have long held: In those depressed patients whose symptoms are so severe they cannot initiate self-help, antidepressant medication may be of benefit. In almost all other instances that is likely not the case. Vindication is a perk this editor both merits and gets to enjoy all too infrequently. ❖

Religiosity and Cardiovascular Disease

ABSTRACT & COMMENTARY

By Howell Sasser, PhD

Dr. Sasser is Associate Professor of Epidemiology, New York Medical College, Valhalla, NY; he reports no financial relationship to this field of study.

Synopsis: *Feinstein and colleagues assessed the association of religious activity with concurrent risk factors for cardiovascular disease, and with later adverse cardiovascular events. They found that those who were more religious were less likely to smoke and more likely to be obese, even after controlling for several other demographic factors. There was no apparent association in their population between religious practice and a reduction in cardiovascular risk.*

Source: Feinstein M, et al. Burden of cardiovascular risk factors, subclinical atherosclerosis, and incident cardiovascular events across dimensions of religiosity: The multi-ethnic study of atherosclerosis. *Circulation* 2010;121:659-666.

A CENTRAL QUESTION IN THE STUDY OF MANY BEHAVIors that appear to have a beneficial effect on health is whether such behaviors make people healthier or simply are attractive to people who are healthier to begin with. This issue has been prominent in the study of religious practice as a modifier of health risk. A number of well-regarded studies have suggested that some aspect of religious activity promotes healthy behaviors and even reduces mortality.[1,2] However, most studies to date have had difficulty determining whether such benefits derive in some way from religion or reflect the composition of the religiously active population, or perhaps from a combination of both.

Feinstein and colleagues add to the literature with a study that was designed to address aspects of this question. Their population, drawn from the Multi-Ethnic Study of Atherosclerosis (MESA), was geographically and racially diverse to permit inferences independent of regional or confessional characteristics. The study design included both cross-sectional and longitudinal elements to help in distinguishing between factors that individuals "brought" to their religious practices and the later impact of religion on health. The investigators also included multiple measures of religious activity rather than one, noting that religiousness is appropriately seen as a complex construct.

From the MESA cohort, 5,474 participants were included in the present study. All were between the ages of 48 and 84 years and free from cardiovascular disease (CVD) when enrolled. Caucasian and African-American participants were included in numbers slightly greater than their representation in the total MESA population; Chinese and Hispanic participants were slightly underrepresented. Anthropometric and behavioral risk factors, including smoking, obesity, diabetes, and hypertension, were collected at the same follow-up visit at which information about religious practices was collected. Measures of subclinical CVD were collected at baseline (coronary calcium score, carotid intima-media thickness, and left ventricular mass) and at a later visit (ankle brachial index). Religious practice was also assessed at this visit. Follow-up for new, clinically apparent cardiac events averaged 4.1 years, and collected information on death, myocardial infarction, and hospitalization for unstable angina.

Religious activity was defined by frequency of participation in public religious services, frequency of prayer or meditation, and "spirituality," as defined by responses to five questions drawn from the Daily Spiritual Experiences Scale. The participation and prayer measures were scored as Never/Once or Twice per Year/Monthly/Weekly/Daily, and the spirituality measure, summed over the five questions, as None/Low/Moderate/High.

The authors noted that results for the measures of religious attendance and prayer were very similar and presented only those for religious attendance. Participants who were more religiously active and those who reported higher levels of spirituality were more likely to be older, female, and African-American. They also were more likely to be obese and hypertensive, and less likely to smoke. The higher prevalence of obesity and lower prevalence of smoking among more intensely religious participants remained statistically significant after adjusting for demographic factors. More intensely religious participants also remained statistically more likely to be obese after adjusting for demographic factors and smoking status. No consistent and statistically significant associations of religious behavior with markers of subclinical CVD or new cardiac events were found.

■ COMMENTARY

Feinstein et al provide mixed results, some of which confirm earlier findings and some of which do not. The higher prevalence of obesity and lower prevalence of smoking among more religiously active people are both well characterized.[3,4] An interesting innovation in this respect is the finding that obesity is independent of other factors including smoking, prompted by the authors' observation that cigarette smoking has a role in appetite suppression. The finding of no association between religious activity and lower rates of negative health events is not in agreement with many earlier studies, but is also tied to a specific category of events, while prior studies often have used a more general model, such as all-cause mortality. This negative finding elicits from the authors relatively little discussion beyond a call for further research to determine whether their results can be replicated.

Readers should note several factors in the design of this study that have an impact on its interpretation. First, while the study collected a number of relevant demographic and lifestyle variables, it lacked measures of physical activity and of psychosocial stress, each of which is significant in heart disease, as well as in the most salient risk factors in this population — smoking and obesity. Stress is also hypothesized to be a mediating factor in the relationship of religious activity with health.[5,6] These omissions leave open the possibility of unmeasured confounding.

Second, while the population was racially and ethnically diverse, it was arguably not religiously diverse. Inference from the ethnic make-up of the sample would suggest that it was mostly Christian with a small number of practitioners of East Asian religious and philosophical systems (Buddhism, Daoism, Confucianism). A wider range of religious traditions would be desirable, both to allow more stable comparisons and to represent the variety of expectations with respect to attendance at public religious activities and ways of expressing spirituality.

Third, to the study's credit, it collected several measures of subclinical disease. A chicken-and-egg dilemma in research on religious activity is the role of chronic, preclinical disease in motivating such behavior. If those with subclinical disease are more prone to adopt religious coping strategies, one might expect more clinically relevant later health events among religious people. This study showed some differences in preclinical CVD by level of religious activity, but no consistent pattern. This adds weight to the study's other findings.

Finally, this and all other studies of religion and health continue to grapple with how best to conceptualize and measure a complex concept that often is poorly explored, even at the individual level. The demand for quantification continues to favor the use of measures that permit uniform counting (i.e., how often) at the expense of measures of intensity. This leaves unanswered the basic question of whether religiousness is being measured — or even understood — correctly. ❖

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5. Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: A review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress* 2009;12:1-21.
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CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe evidence-based clinical analyses of commonly used integrative therapies;
- make informed, evidence-based recommendations about the usefulness and efficacy of integrative therapies to patients in their practice; and
- critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in integrative medicine as published in the scientific literature.

Omega-3s and Old Age: Fish Oil and Telomere Length

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *Results of this longitudinal observation study reveal that, in people with stable coronary artery disease who were followed for 5 years, baseline levels of omega-3 fatty acids were inversely related to*

CME Questions

14. Curcumin research has implied that this substance might have therapeutic potential in which of the following diseases?

a. Alzheimer's
b. Cancer
c. Malaria
d. Depression
e. All of the above

15. Curcumin, taken orally, has shown a high bioavailability, which explains its actions in tissues distant from the GI tract.

a. True
b. False

16. Which of the following statements is *not* true regarding the treatment of depression?

a. Effectiveness of acupuncture and amitriptyline is similar.
b. Antidepressant medications are associated with significant side effects.
c. Most depression studies have focused on people with severe symptomatology.
d. Antidepressant medication was superior to placebo regardless of depression severity.

Answers: 14. e, 15. b, 16. d.

leukocyte telomere length, the latter a unique marker of aging. The authors conclude that high omega-3 fatty acid levels may protect against cellular aging. The study was well done, but the results may not be widely generalizable.

Source: Farzaneh-Far R, et al. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA* 2010;303:250-257.

THE RESEARCHERS BEHIND THIS PROSPECTIVE COHORT trial sought to determine whether omega-3 fatty acid levels (n-3 levels) were associated with temporal changes in leukocyte telomere length over 5 years in outpatients with known coronary artery disease (CAD). Subjects were recruited from the Heart and Soul Study (a prospective cohort trial examining the influence of psychosocial factors on cardiovascular events in stable CAD). A total of 1,024 subjects enrolled in the study by 2002. At baseline, demographic information was collected, exercise capacity was determined, medication use detailed, and waist and hip circumference measurements performed. At the same time, participants had blood drawn for lipids and C-reactive protein, and measurements of n-3 levels and baseline telomere length performed. Resting 2-D echocardiography and Doppler examination were also performed, and left ventricular ejection fraction calculated.

Five years later all participants were invited to return for repeat examination. Complete data were available for evaluation on a total of 608 subjects with a median follow-up of 6 years (range, 5.0-8.1 years). Subjects and their n-3 levels were categorized by quartiles. In the quartile analysis, there was no significant association between baseline n-3 levels and baseline telomere length; however, baseline n-3 levels were positively correlated with 5-year change in telomere length. Subjects in the lowest quartile of n-3 levels experienced a decrease in telomere length of 0.13 T/S units, whereas those in the highest quartile experienced a decrease of only 0.05 T/S units ($P < 0.001$ for trend). In the unadjusted linear regression model, higher baseline log n-3 levels were associated with an increase in absolute telomere length over time. This association withstood sequential adjustment for a wide variety of potential confounding factors.

A total of 45% of subjects exhibited > 10% reduction in telomere length. Each 1-SD increase in baseline log n-3 level was associated with a 19% decrease in the odds of telomere shortening. After adjustment for potential confounders, each 1-SD increase in baseline log n-3 level was associated with a 32% decrease in the odds of telomere shortening.

The authors conclude that baseline levels of n-3s were inversely associated with telomere attrition over 5 years, an association that was linear and persisted after adjustment for potential confounders; thus, they say, n-3s may protect against cellular aging in people with stable CAD.

■ COMMENTARY

Most professionals, even most of the lay public, are aware of the potential health benefits associated with regular consumption of cold water fish or fish oil supplements. Published data strongly suggest a protective effect against second acute coronary events, dysrhythmias, elevated triglyceride levels, and vascular inflammatory changes, not to mention potentially beneficial effects in other clinical settings. But what sets this study apart is the measured effect on telomere length, a unique marker of aging that a growing number of experts seem to have confidence in. The mechanism of action of n-3s remains unknown at this time, but the conclusion seems inescapable that n-3s help modulate aging and age-related dysfunction. The current study utilized multivariable analysis and successfully discounted potential confounders, but as the authors note, there are many influences on telomere length beyond n-3s. One significant shortcoming — the majority of subjects were male.

The results of this study further underscore the importance of omega-3 fatty acids in the prevention and treatment of CAD, but keep in mind the results represent an observation, not necessarily cause and effect. ❖