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Intercessory Prayer for Healing: Looking at the Studies

By Dónal P. O'Mathúna, PhD

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In September 2010, the most recent study of intercessory prayer was published in the *Southern Medical Journal*.[1] The researchers suggested that the key to prayer's effectiveness was proximity between the person praying and the one prayed for. The study followed 24 Mozambican subjects who received intercessory prayer for hearing and/or vision problems. Although significant improvements were reported, the study did not have a control group, it was not double-blinded, and challenging field conditions led to deviations from the protocol.

This study is the latest is a series of scientific investigations of prayer that can be traced back to the Irish physicist John Tyndall.[2] In 1872, Tyndall proposed that all Christians should pray for the patients of one particular ward or hospital for at least 3 years. Skeptical of Christianity, he believed that patient outcomes would be no better in that hospital compared to other hospitals and this investigation would provide scientific evidence that prayer is ineffective.

The experiment was never conducted, but it generated controversy on both sides of the Atlantic and has become known as the Prayer-Gauge Debate.[3] Francis Galton, a cousin of Charles Darwin, noted that people pray frequently for clergy and royalty. He suggested that the records be examined to see whether those receiving these prayers lived longer, happier lives. He found that those prayed for lived shorter lives than "less noble" professionals. Galton believed this was evidence that prayer doesn't work.

The topic received little attention for several decades until 1988, when the *Southern Medical Journal* published a study by Randolph Byrd.[4] This high-quality controlled trial enrolled coronary care unit patients and randomized them to either control or daily prayer. This was the first of several large randomized controlled trials (RCTs) that have been published over the past two decades.

Part of the reason for these studies may be that in surveys of complementary and alternative medicine, prayer consistently tops the

Summary Points

• Several controlled studies of prayer have been conducted over recent decades.

• Much variability exists in the design, interventions, and results of these studies.

• Patients can be reassured that their belief in prayer has not been undermined by scientific studies, and that prayer remains a faith-based practice, not one based solely on scientific research.

lists. Prayer was the most frequently used therapy in the three large surveys carried out by David Eisenberg and colleagues at Harvard Medical School. The proportion of U.S. adults using prayer was 25%, 35%, and 45% in 1990, 1997, and 2002, respectively.[5] The most recent survey, published in 2005, collected more detailed information on prayer. Although in general prayer was the most popular "therapy," used by 45% of respondents, 43% prayed for their own health (making it the second most popular therapy), 24.2% had others praying for their health (the third most popular therapy), and 9.6% participated in a prayer group (the sixth most popular therapy). Given such prevalent use, it would make sense that researchers try to establish whether or not it is effective. Clinicians should be aware of this evidence so they can discuss it with patients. Given that prayer often is a deeply personal practice, patients may want to discuss the implications of this research for their own health and well-being.

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Searching the Literature

Viewing prayer as a therapy is problematic for some. Prayer can be an expression of someone's personal relationship with God, not a therapy to be used only when needed. Such contemplative prayer is different from what usually is tested in scientific studies.[6] Intercessory prayer is more amenable to research because the person praying is usually different from the one prayed for.

Controlled studies of intercessory prayer for health and healing in humans will be reviewed here. A total of 28 published trials of intercessory prayer were located. Although most studies have examined various types of Christian prayer, other practices have been included. These include Jewish, Buddhist, and various esoteric practices. These studies can be divided into three general groups:[2]

- Small studies examining physical conditions (eight studies)
- Studies of psychological conditions (six studies)
- Higher quality studies of physical conditions (14 studies)

It would be challenging to combine the results of these studies due to their different designs and outcomes. Rather than discuss all the studies, two sub-groups will be examined as characteristic of the whole group. The first includes some of the best studies, while the second includes the worst.

Randomized Studies with Cardiac Patients

A number of larger RCTs have been published in recent years. The first of these, by Randolph Byrd, randomized 393 coronary care unit patients to either control or daily prayer from "born-again" Christians.[4] Between three and seven people prayed for each patient for a rapid recovery and prevention of both complications and death. No significant differences between the two groups were found on those outcomes. Twenty-six other medical outcomes were measured, with the prayer group having significantly better results in six. A tool for ranking patients' overall outcome was developed (but not validated), and showed the prayed for patients did significantly better ($P < 0.01$).

Byrd's study was replicated in 1999 with 990 coronary care unit patients.[7] Those randomized to the prayer group received Christian prayer for 28 days. Thirty-five medical outcomes were examined, with no significant differences on any individual measure. Using Byrd's tool no significant differences in overall outcome were found, but a tool developed (but not validated) by these researchers found significant improvements ($P = 0.04$). The prayer group scored 11% better than the control group, but the researchers questioned the clinical significance of this.

A third RCT was published in 2001.[8] As 799 patients were being discharged from a hospital coronary care unit, they were randomly assigned to receive prayer or not.

People from religious and community groups volunteered to pray for each patient at least once a week for 26 weeks. No significant differences were found between the two groups in various measures of cardiac health.

The Monitoring and Actualization of Noetic Training (MANTRA) research project produced results after a pilot study and the complete study. The pilot project was cited widely because it had "encouraging" results, but these were not statistically valid because of the small number of participants.[9] The ensuing RCT randomized 748 patients scheduled for cardiac catheterization.[10] Patients first were assigned randomly to no prayer or to receive prayer from Christian, Jewish, Buddhist, and Unity Church groups. Then, all participants were randomized to receive either no additional complementary therapy or a combination of music, relaxed breathing, guided imagery, and Healing Touch. No statistically significant differences were found between the four groups for the primary outcomes measured.

The largest RCT of prayer to date was led by Herbert Benson and was published in 2006.[11] In the Study of the Therapeutic Effects of Intercessory Prayer (STEP), 1,802 cardiac bypass patients were assigned to one of three groups. One was a control group and two groups received intercessory prayer from various Christian denominations. The two groups receiving prayer differed as one group knew they were being prayed for while the other group did not know whether they were receiving prayer or not. These groups were included to examine the role of suggestion. The primary outcome was the occurrence of complications after coronary artery bypass, which was not influenced by prayer. However, those who knew they were being prayed for had a higher complication rate than those who did not know the group to which they had been assigned ($P = 0.025$).

Problematic studies

Scientifically studying prayer has been controversial in itself, but a couple of studies have been particularly problematic. In 1998, a study with 40 AIDS patients randomly assigned them to either a control group or to receive psychic, shamanistic, Jewish, Christian, and Buddhist prayer.[12] Of the 11 outcomes measured, those prayed for did significantly better in 6. However, after one of the researchers died, an investigative reporter discovered that the researchers had changed their protocol during the study and run different series of calculations that had not been planned originally.[13] The data also were examined after blinding had been broken, but none of this was discussed in the original publication of the study results.

The controlled study of prayer with the most clearly beneficial results involved patients using in vitro fertilization.[14] Those being prayed for had double the pregnancy rate of the control group ($P = 0.001$). However, one of the authors since has withdrawn his name from the publication.[15] The author who organized the study, Daniel Wirth, has been jailed for fraud unrelated to this project, but this has cast a shadow of doubt over all his research.[16] His supervisor and former colleagues have appealed publicly to him to clarify which of his publications are authentic.[17] Two of the other small prayer studies were conducted by Wirth, who has not responded publicly to date.

Conclusion

Many of the early prayer studies were poorly designed and had few subjects. Most of the psychological studies were similarly small and had inconsistent results. The larger cardiac studies discussed here exemplify the current difficulty in reaching scientific conclusions about prayer studies. Individual outcomes sometimes show significant improvements in the prayer group, but for the most part the overall differences are not significant. The problematic studies add another level of concern to some of this research. Perhaps because this research raises questions about the relationship between religion and science, it may remain challenging.

Prayer studies can leave people with difficult or disturbing questions about whether science has proven or disproven the power of prayer. The inconsistency in these results shows that prayer studies have not provided a clear answer. However, some conclusions can be reached. If prayer involved an impersonal energy or subtle human energy, better research would be expected to reveal more consistent results. The results do not support this view of prayer. If, on the other hand, prayer involves a personal God who chooses how to answer, controlled studies will never be conclusive.[2] Randomized, double-blind studies can control for the placebo effect, but not for divine choice. Within this view of prayer, inconsistent results are what would be expected.

Prayer will remain based on people's beliefs and not clinical evidence. Decisions about whether or not to pray always will remain in the area of personal faith and not scientific evidence. Scientific inquiry can shed light on many health questions, including some related to prayer. Studies can fruitfully investigate the experiences of those who pray and whether they report better outcomes than those who do not. But in many prayer studies, attempts to avoid religious issues have led to compromises that distort either the science or the religion. The cardiac studies emphasized scientific rigor, but failed to recognize the impossibility of controlling divine forces. The Mozambican study remained faithful to the religious practice, but compromised on scientific rigor.[1] Science has its limits, and studying prayer as a controlled intervention exceeds one of them. ■

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The Role of Spirituality in Physician–Patient Interactions

The Reverend Dr. Howell Sasser, PhD

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RECENT DECADES HAVE SEEN A DRAMATIC EXPANSION IN the visibility of ethnic and cultural diversity in the United States. Much of this is not new, only newly prominent. Numerous ethnic, linguistic, religious, and cultural groups have been present in the United States since its beginnings, and even the popular image of a Caucasian Protestant majority includes many variations. A paradoxical consequence of this growing awareness of diversity may be a reluctance to address it directly that is motivated by a wish not to seem ignorant or give offense. Yet failure to do so can itself lead to misunderstandings and bad outcomes, especially in fields like medicine.

While there are numerous relevant aspects to the topic, this article will concentrate on the role of spirituality and religious faith in physician-patient interactions. Even that limitation leaves too large a subject to cover exhaustively, so the goal will be to offer general suggestions that might serve as guides for an exchange of relevant information rather than as precise instructions. For this purpose, it will also be assumed that the encounter in which the subject of spirituality arises is part of—or at least at the beginning of—an ongoing therapeutic relationship. Medical relationships that begin in times of crisis have their own dynamics and deserve separate treatment.

A clinician who wishes to be sensitive to the beliefs and practices of his/her patients would be well advised to begin by considering his or her own. Our reactions to the attitudes and opinions of others are necessarily influenced

Summary Points

• Physicians who wish to be sensitive to the spiritual and religious faith of their patients should first carefully consider their own beliefs.

•.Although medical encounters often are brief, it is important to allow time for patients to share their beliefs.

•. When discussing spirituality with patients, physicians must be prepared to answer questions as well.

by those we carry ourselves, whether conscious or unconscious. Even if after careful consideration, the outcome is, "I don't subscribe to any religious or spiritual practices or beliefs," or, "I don't know what I believe," that insight will help to put anything a patient says into perspective. It is important also to bear in mind that there can be no right or wrong answers in such matters. Belief in a higher being is not intellectually equivalent to believing in the efficacy of antibiotics. The purpose in asking about a patient's spirituality is to incorporate that information into a plan to provide the best medical care possible to the whole person. Differences in belief between physician and patient need not prevent that from happening, but a physician who is unaware of his or her own influences and attitudes may miss or misinterpret important information.

With this understanding in place, the next step is to ask simple, open-ended questions of the patient. Physicians and patients have become conditioned to the asking and answering of all kinds of sensitive questions—about substance use, sexual habits, family dynamics—so questions about spirituality need not seem any more awkward. A question in an intake exam such as, "Do you have any spiritual or religious beliefs or practices that I should know about?" allows for a polite refusal ("No, not really.") or a more complex response. Such questions can easily be made "condition-specific." A visit that focuses on affective issues or a condition in which the response to stress is relevant (for example, hypertension) presents an opening for a question like, "Do you use any practices like meditation to help manage the way you feel?" With older people and those from racial/ethnic groups in which churches or other religious organizations remain strong social institutions, a question about social support may be helpful—"Do you have people at your church who can help you with jobs around the house or with getting to appointments?" This can provide some information about a patient's level of religious involvement, and might also elicit further information about the role of religion as a coping strategy in his/her life.

A seemingly obvious, but important, point is to allow time for answers. Medical encounters are often very brief by necessity, with a large amount of information to give and receive. Efficiency may be predicated on an assumption that answers to questions can be succinct. However, when a patient is asked about his or her approach to spirituality, the answer may be lengthy either because of its complexity or because it requires going into unexplored territory. To ask about it and then have to cut short the answer is perhaps worse than not to ask at all. A patient's description of his/her beliefs and practices also may be aided by a few prompts. If something is not clear or could have multiple interpretations, do not hesitate to say, "I'm not sure I understand that." Summarizing what the patient has said, often aided by the expression, "What I hear you saying is…," can also help avoid misunderstandings.

Don't expect to get the full story all at once. A significant portion (perhaps a majority) of actively religious people in modern America are reticent about discussing their faith in one-on-one encounters with others whom they suspect may not share them. In the case of medicine, this may be because physicians are widely viewed as being drawn from—or educated into—a social and educational class that is dismissive of religion ("followers of Scientism"). This view, coupled with the message, communicated in many ways, that physicians' time is very limited, may constrain or sanitize what is said. The same strategies for overcoming such concerns about other issues are useful here—being at eye level, avoiding negative body language, using visual and vocal cues to indicate interest.

Be prepared to answer questions as well as ask them. Part of making a patient feel comfortable discussing his or her faith is being willing to go wherever the conversation leads. It may be to the personal ("And what do you believe?") or the more theoretical ("What did I do to deserve to be this sick?"). The latter sort of question is often rhetorical, but a response in the form of a question like, "What does your religious tradition teach about that?" can elicit valuable information and almost always will be well received.

Be sure to make a few notes. Information obtained at a routine or low-acuity visit may usefully be brought up again later. When a time of more serious illness arises, a question like, "Do you have someone praying for you?" may both remind the patient of the earlier conversation and put him/her at ease in talking about it now. It is a common observation of the clergy that religious faith serves as a "fallback" resource for many more people than attend services regularly. Such a question, asked in a time of stress, is unlikely to be viewed as offensive. At the same time, it is important for the physician to consider in advance what reply to make if the answer is "no." In this, as in other situations, sincerity and assurance that the physician is in a "therapeutic alliance" with the patient are more important than empty words.

These suggestions are intended as points of departure. Variations in geography, local culture, practice patterns, and concordance or discordance in physician-patient age or race/ethnicity, among many other factors, will influence whether and how to bring religion or spirituality into the clinical picture. At a personal level, a physician's comfort with the subject will also drive such choices, though ironically, this may be the part of the equation over which the individual physician has the most control. Careful consideration of one's own past and present circumstances, combined with an open and nonjudgmental style with patients, can yield much that will be of diagnostic and therapeutic value. ■

Tai Chi for Fibromyalgia: Marshalling the Art of Movement Against Pain

ABSTRACT & COMMENTARY

By Nancy J. Selfridge, MD

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Synopsis: *Fibromyalgia patients were randomized to a treatment protocol consisting of 12 weeks of tai chi instruction and practice or a control intervention of wellness education and stretching exercises also of 12 weeks duration. The tai chi treatment group demonstrated clinically significant improvements in pain and quality of life compared to the control group and these improvements were maintained at 24-week follow up.*

Source: Wang C, et al. A randomized trial of tai chi for fibromyalgia. *N Engl J Med* 2010;363:743-54.

The investigators in this NCCAM-funded study hypothesized that 12 weeks of tai chi training and practice would prove beneficial for fibromyalgia patients at reducing pain, improving sleep quality, and improving physical and psychological function compared to a control intervention of wellness education and stretching exercises. Sixty-six patients who met the 1990 ACR diagnostic criteria for fibromyalgia were randomized into a tai chi group (n = 33) or a control group (n = 33).[1] Subjects who had participated in tai chi training or classes within the prior 6 months were excluded as were those with comorbidities known to contribute to fibromyalgia symptoms, e.g., inflammatory arthritides, vasculitides, myositis, or thyroid disease.

The tai chi intervention consisted of twice weekly 60-minute sessions for 12 weeks. A single teacher, a tai chi master, taught all classes at a single venue. Tai chi principles of movement, breathing, and relaxation were preceded by a warm-up and self-massage. For the intervention period, participants also were instructed to practice tai chi at home for at least 20 minutes each day. At the end of the 12-week period, participants were encouraged to continue their tai chi practice on their own using an instructional DVD.

The control intervention also consisted of twice weekly 60-minute sessions for the 12 weeks. Each session was composed of a 40-minute didactic presentation by a health professional on a topic related to fibromyalgia, e.g., optimal nutrition, pain management, sleep problems, exercise, and coping strategies. The final 20 minutes of each class was devoted to practicing supervised stretching. Control group participants were similarly encouraged to practice the stretching exercises at home for 20 minutes each day.

All participants were encouraged to continue their routine medications, activities, and medical care throughout the study period. Adherence to the programs was assessed by monitoring class attendance, providing make-up classes for missed sessions, and having participants complete daily logs documenting their home practice or stretching. To minimize the placebo effect of the tai chi intervention, participants in both groups were told that the purpose of the study was to compare two different exercise programs, one with an educational component and one without.

The primary outcome measure was a change in the Fibromyalgia Impact Questionnaire (FIQ) score from baseline to the end of the 12-week study period. Secondary outcome measures included a weekly FIQ score; global pain status using a visual analog scale (VAS) by the study participant and the study physician who was blinded to the group assignment; and a tender point count by the same physician. Participants' physical performance was measured using a 6-minute walk test (the number of yards walked in 6 minutes). Additional standardized instruments were used to assess sleep quality, depression, outcome expectations for exercise, and self efficacy. The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to measure physical and mental quality of life. Any changes in medication use were documented. All measures were repeated at a 24-week follow-up visit to test durability of response. Both groups had similar baseline characteristics and scores except for the Center for Epidemiologic Studies Depression (CES-D) index; the tai chi group had a lower mean score indicating less baseline dysphoria.

All data were subjected to intention-to-treat analyses. Participants who did not complete the follow-up period (tai chi group n = 3; control group n = 4) were considered not to have any changes in scores. Potential interactions between treatment and the covariates of age, sex, BMI, duration of symptoms, pain severity, coexisting illness, and medication use were tested.

Significantly more patients in the tai chi treatment group had clinically meaningful changes in their FIQ scores compared to the control patients: 79% vs. 39% (P = 0.001) at 12 weeks and 82% vs. 51% (P = 0.009) at 24 weeks. Tai chi participants also met standards for clinically meaningful improvement in VAS pain scores, sleep quality, depression, and SF-36 scores more often than controls. These treatment effects remained significant even after adjusting for the group baseline differences in scores for depression. Additionally, more patients in the tai chi group had discontinued medication at 12 weeks compared to the control group, though the difference was not statistically significant.

■ COMMENTARY

Studying complex mind-body interventions such as tai chi for equally complex pain conditions such as fibromyalgia is fraught with challenges. A main limitation of this study is that it was single-blinded, as no validated sham tai chi protocol currently exists. However, the investigators may have been successful at de-emphasizing the tai chi intervention (and a potential placebo effect) in the way that participants were informed of the purpose of the study. At least at baseline, both tai chi and control group scores for outcome expectations of benefit from an exercise intervention were similar.

One shortcoming of the study is that although no adverse events were reported, post-exercise delayed muscle soreness was considered an expected outcome and thus was not considered a reportable adverse event. Many fibromyalgia patients cite such soreness as a reason for not being able to exercise. Class attendance was 77% for the tai chi group and 70% for the control group. This level of non-adherence is not atypical for fibromyalgia patients engaged in exercise programs[2] but it does beg the question as to whether fibromyalgia patients' post-exercise soreness is as problematic with tai chi as it is for other forms of exercise.

Since 51% of the patients in the control group showed clinically meaningful improvement in FIQ scores at 24 weeks it would be interesting, albeit difficult, to tease out which elements of tai chi created the added advantage. Though double-blind, larger, and longer-term studies are needed to determine the generalizability of this study's positive findings, there is no reason for a practicing clinician not to add tai chi to a growing non-pharmaceutical armamentarium against fibromyalgia pain and debilitation. ■

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'B' Sharp? Alzheimer's Disease and B Vitamins

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Source: Smith AD, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. *PLoS One* 2010;5:e12244.

Synopsis: *Results of this methodologically sound trial strongly suggest that moderate-dose B vitamin therapy has a protective effect against the rapidly progressive brain atrophy commonly seen in elderly people with mild cognitive impairment (MCI). The intervention was safe and effective over a 2-year time frame, and shows promise for slowing the inexorable progression of MCI to frank dementia.*

The researchers behind this British single-center, randomized, controlled, double-blind trial sought to determine whether high-dose B vitamin supplementation could slow the rate of brain atrophy in subjects age 70 years or older with mild cognitive impairment (MCI) over a 2-year period. The data come from what has been called the VITACOG trail.

Elderly people with concerns about their memory were recruited for screening through local advertisements. Inclusion criteria included a diagnosis of MCI with corroborative results on tools such as the Telephone Interview of Cognitive Status, Modified (TICS-M) and Mini-Mental State Exam (MMSE). Exclusion criteria included a prior diagnosis of dementia, recent stroke, or the taking of high-dose B vitamin therapy (those using low-dose B vitamins were permitted to continue and participate in the study). Subjects were randomized to receive either placebo or high-dose B vitamin therapy (0.8 mg folic acid, 0.5 mg cyanocobalamin. and 20 mg pyridoxine HCL). Tablets were provided at time of initial study entry and

subsequently by mail at 6-month intervals.

Volumetric cranial MRI scans were performed at baseline and at trial's end (2 years). An automated, quantitative, proven method (SIENA) was used to measure rate of whole brain atrophy, the main outcome of interest. Primary analysis focused only on those subjects for whom a technically good MRI was available both at baseline and at ~24-month follow-up (n = 83 placebo, n = 85 B vitamins group). All subject analyses were adjusted for age because the factor was strongly associated with rate of brain atrophy.

Secondary outcomes included adverse events, withdrawals, compliance, changes in biochemical markers, and cognitive and depression scores (the authors will be reporting results of the latter in a separate publication). Total homocysteine and plasma vitamin levels were determined and compliance levels defined.

At the end of the trial, adherence to protocol was noted to be good as determined by the number of returned tablets and plasma vitamin concentrations. A total of 48 subjects were lost to follow-up (n = 20 in placebo group). No significant difference in adverse effects was found save for a slightly lower number of subjects in the active group who lost vibration sense.

Plasma total homocysteine increased by 7.7% in the placebo group and decreased by 31.7% in the active group. The rate of brain atrophy slowed significantly with B vitamin therapy, being 29.6% less than the rate determined for placebo group subjects. A significant interaction was found between baseline homocysteine levels and treatment effect in the placebo group, with higher homocysteine levels associated with a higher rate of brain atrophy. As plasma homocysteine concentrations decreased, the rate of brain atrophy likewise decreased. In addition, the rate of brain atrophy slowed as concentrations of folate and B_{12}, but not B_6, increased. On the other hand, those subjects whose folate and B_{12} levels decreased over the two-year period were found to be at increased risk for brain atrophy. Of note, subjects in the placebo group with a prior history of stroke or TIA at baseline had an increased rate of brain atrophy compared to people without such a history; the rate of brain atrophy was slowed in subjects with a history of CVA or TIA who received B vitamin therapy.

When total homocysteine results were divided into quartiles, no effect of B vitamin therapy was detectable for those in the lowest quartile (total homocysteine $\leq$ 9.5 µmol/L), whereas there was a 53.3% decrease in brain atrophy rate in those subjects in the highest quartile (>13.0 µmol/L) treated with B vitamins. Treatment effect was thus greatest for those with the highest baseline homocysteine levels.

In a post hoc analysis the researchers found that final cognitive test scores were positively correlated with rate of brain atrophy.

The researchers concluded that the accelerated brain atrophy seen in elderly people with MCI can be slowed with high-dose B vitamin treatment that lowers homocysteine levels, potentially slowing progression to Alzheimer's disease or other forms of dementia.

■ COMMENTARY

The authors note that between 14-18% of people older than age 70 years, or approximately 5 million people in the United States, have MCI , and about half will go on to develop dementia. They also note that while elderly people typically experience significant and progressive brain atrophy, even those who are cognitively healthy, a much-accelerated form of brain atrophy occurs with Alzheimer's disease. An intermediate pace of brain atrophy is seen in people with MCI, but a more rapid rate is characteristic of subjects with MCI who convert to Alzheimer's disease. Effective means to reduce the rate of brain atrophy might slow progression to Alzheimer's disease.

Experts believe the number of cases of Alzheimer's disease likely will rise dramatically within the next decade. Preventive interventions are urgently needed because there is no cure for the disease. The prescription aids currently available only slow the progression of cognitive dysfunction, not halt or reverse it. Unfortunately, there is scant evidence on effective preventive strategies. Following a Mediterranean-style diet appears to offer some protection, and regular physical and mental exercise, and perhaps the use of specific anti-inflammatory agents, all show at least a modicum of promise, but there is little agreement on tactics beyond these basics.

A great deal of study has already taken place regarding homocysteine and homocysteine-lowering therapies, especially B vitamin therapy, and select disorders. Research into the use of B vitamin therapy to reduce cardiovascular risk largely has not met high expectations, but elevated homocysteine levels are a recognized risk factor for brain atrophy, cognitive impairment, and Alzheimer's disease, and it is well-accepted that plasma levels of homocysteine can be lowered through dietary administration of B vitamins. It appears, however, that a beneficial effect can be anticipated only for those with a high baseline total homocysteine concentration (> 9.5 µmol/L). It is noteworthy that the current study took place in the United Kindgom, where fortification of foods with folic acid is not mandatory.

Prior studies have shown that the rate of whole brain atrophy in MCI correlates with cognitive decline as measured by several different tests, including MMSE, and that the rate of atrophy may be a major determinant of final MMSE and TICS-M scores. The authors' data re-

garding cognitive and depression scores should be very interesting and, hopefully, compelling.

This well-done study raises hopes that moderately high-dose folic acid and B_{12} therapy, though perhaps not pyridoxine, may offer some protection against rapid brain atrophy in elderly people with MCI. The intervention appears to be safe and to have a meaningful clinical effect. Yes, more data are required, but for elderly patients with MCI, B vitamin therapy should be a therapeutic consideration, save for the presence of a specific contraindication. ■

Not the Same Old Thing—SAMe for Depression

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *A unique study pairing the use of a standard SSRI and SAMe against major depression in subjects who had not responded adequately to SSRI monotherapy suggests safety and significant efficacy over a 6-week trial period.*

Source: Papakostas GI, et al. S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: A double-blind, randomized clinical trial. *Am J Psychiatr* 2010;167:942.

In the face of a rising prevalence of major depression, troubling answers to questions about the efficacy and safety of pharmaceutical antidepressant therapy, and concern over rates of non-response to antidepressant therapy, the authors of this double-blind, randomized, controlled trial investigated the use of SAMe as additive, augmentative treatment for people with major depressive disorder who had not responded fully to SSRI antidepressant therapy. A single-center randomized, double-blind controlled trial was performed over the course of 6 weeks. Adult subjects had to meet DSM-IV criteria for current major depressive disorder, have a Hamilton Depression Rating Scale (HAM-D) score of at least 16 at both screening and baseline visits, have been treated with an SSRI at adequate dose for at least 6 weeks' duration, and have been taking a stable dose of SSRI for the prior 4 weeks. Subjects with a history of suicidal ideation or mania were excluded.

Participants were randomly assigned to receive either SAMe 400 mg twice daily or matched placebo. Study visits occurred weekly for a total of 6 post-baseline visits. Following the second post-baseline visit, all subjects had their number of pills doubled for the duration of the trial so that they were then ingesting two pills twice daily (1,600 mg of SAMe or 4 placebo pills). SSRI doses remained constant during the 6-week study. HAM-D and Clinical Global Impression (CGI) severity and improvement scales were administered at each visit. Primary outcome measure was difference in response rates between the two treatment arms according to HAM-D ratings. A positive response was defined as ≥ 50% reduction in scores during treatment (or a final score ≤ 7). Secondary outcome measures of interest included continuous change in HAM-D scores and CGI severity ratings during treatment.

A total of 73 subjects underwent randomization (n = 39 in SAMe group) with 55 (75.3%) completing the trial (70.5% of placebo and 79.4% receiving adjunctive SAMe). Per HAM-D ratings, response rates for the SAMe- vs. placebo-treated patients were 36.1% and 17.6%, respectively, and remission rates 25.8% and 11.7%, respectively. Differences were statistically significant and considered clinically meaningful.

A slightly higher mean systolic blood pressure was noted for patients receiving adjunctive SAMe compared with placebo (mean difference = 3.1 mm Hg), as well as a nearly significant difference in weight for subjects on SAMe compared with placebo (members of both groups lost weight during the trial but those in the placebo group lost ~1.5 pounds more). There were no serious adverse events, including no episodes of serotonin syndrome (a concern commonly noted with SAMe).

The authors conclude that their preliminary data suggest SAMe to be a safe and effective add-on therapy to SSRIs for the treatment of resistant major depressive disorder, and call for additional studies of SAMe.

■ COMMENTARY

This is the point where the editor of *Alternative Medicine Alert* typically takes his turn appraising the study in question, and offers an opinion on whether or not the results merit clinical consideration; however, in the same edition of *The American Journal of Psychiatry* appears an excellent editorial[1] by J. Craig Nelson, MD, that would be extremely difficult to improve upon and is recommended reading. Nelson notes that there is a paucity of options available when considering adjunctive therapy for people with major depressive disorder who have not responded well to SSRIs. He also points out that upwards of 50% of patients treated with SSRIs may not respond adequately.

A review of the current state of the literature regarding SAMe monotherapy against depression follows, much of which focuses on parenteral therapy, and to a smaller degree oral therapy. In both instances active treatment was shown to be superior to placebo, and comparative trials typically performed with tricyclic antidepressants as the comparator generally showed SAMe therapy to be equivalent in efficacy.

SAMe is a methyl donor that may play an important role in supporting phospholipid cell membrane integrity and optimal production of catecholamines. SAMe crosses the blood-brain barrier, and some data suggest a role for the agent in hepatic disorders and arthritides.

Although the study results are compelling, the few shortcomings are important, the most noteworthy being the significant dropout rate that occurred over the relatively short time frame of 6 weeks, even considering the fact that intention-to-treat analysis was performed.

Confidence in the safety and effectiveness of many antidepressant therapies seems to be falling both among patients and practitioners. On the upside, there has been a growth in interest in other means of preventing and treating mild-to-moderate depression including dietary and fitness methods. Available data suggest SAMe may be a useful stop-gap, if not long-term therapy, because it works relatively quickly when effective. Results like those from the current study serve notice that SAMe might be a useful adjunct to conventional medical care in the treatment of major depressive disorder, a unique role for an intervention until recently considered squarely alternative in nature. ■

Reference

1. Nelson JC. S-Adenosyl methionine (SAMe) augmentation in major depressive disorder. *Am J Psychiatry* 2010;167:889-891.

Low-dose Aspirin to Prevent Preeclampsia

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Dr. Hobbins is Professor, Department of Obstetrics and Gynecology, University of Colorado Health Sciences Center, Denver; he reports no financial relationship to this field of study. This article originally appeared in the October 2010 issue of OB/GYN Alert. *At that time, it was peer reviewed by Catherine LeClaire, MD. Dr. LeClaire is Associate Professor, Department of OB/GYN, Oregon Health and Science University, Portland; she reports no financial relationship to this field of study.*

Synopsis: *Low-dose aspirin, given before 17 weeks, significantly decreases the risk of preeclampsia, severe preeclampsia, IUGR, and preterm birth, compared with its effect when given after that time.*

Source: Bujold E, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: A meta-analysis. *Obstet Gynecol* 2010;116:402-414.

Many clinicians are reluctant to give low-dose aspirin (LDASA) to pregnant women for the prevention of preeclampsia. This reluctance is not based on a fear of potential risk, but on inconsistent study results regarding the efficacy of ASA. Generally, the normal two-stage trophoblastic invasion of the placental spiral arteries is complete by 18-20 weeks of gestation. However, in preeclampsia this trophoblastic remodeling does not happen. The rationale for using LDASA is anchored in the concept that the use of ASA can encourage placental remodeling by altering the relationship between thromboxane and prostacyclin. However, initially, results from randomized clinical trials (RCTs) evaluating patients at risk for preeclampsia or intrauterine growth restriction (IUGR) had not uniformly shown benefit.

Bujold et al, invoking the adage "the earlier the better," reviewed the recent literature and found 12 studies where there was information regarding patients who were randomized to LDASA or placebo at or before 16 weeks and another 22 studies where randomization occurred after 16 weeks. The analysis involved 11,348 women at risk for preeclampsia (a previous history of preeclampsia, IUGR, hypertensive disease, and/or those with abnormal uterine artery waveforms).

Those getting LDASA at or before 16 weeks had a reduction in preeclampsia by half (odds ratio [OR], 0.47; 95% confidence interval [CI], 0.34-0.65) compared with those who received LDASA after 16 weeks of gestation (OR, 0.81; 95% CI, 0.63-1.03). An impressive difference was noted for severe preeclampsia in those getting LDASA at or before 16 weeks (relative risk [RR], 0.09; 95% CI, 0.02-0.37), compared with those who received LDASA after 16 weeks (RR, 0.26; 95% CI, 0.05-1.26). Also, there were significant and dramatic reductions in the incidence of preterm birth and IUGR when LDASA was given at or before 16 weeks, compared with after 16 weeks.

■ COMMENTARY

The concept of heading preeclampsia off at the pass with LDASA has been around for many years, and was the subject of two large NICHD perinatal network RCTs, one in low-risk patients[1] and the other in high-risk patients.[2] The results were inconclusive, but when data from the second study were pooled with those from later studies,[2] benefit was demonstrated, especially in preventing severe preeclampsia. The Bujold et al study strongly suggests that the early administration of LDASA is the best approach to preventing adverse pregnancy outcome.

So — who would benefit most from LDASA?

1. Patients at historical risk for adverse pregnancy out-

come would include those with a history of preeclampsia, pregnancy-induced hypertension, abruption, and IUGR, where the bulk of "high-risk" studies and the meta-analyses by Coomarasamy[3] and Bujold have shown benefit, especially if used early.

2. Patients with abnormal uterine artery wave forms. Interestingly, although initial study results have been inconsistent regarding the ability of using uterine arteries to predict preeclampsia, recent data have shown its use in high-risk patients to have very reasonable efficacy in predicting preeclampsia and IUGR.[4-6] Coomarasamy et al published a meta-analysis of RCTs involving the use of LDASA in patients with abnormal second trimester uterine artery waveforms and found a statistically significant halving of preeclampsia and, although not significant, it added, on average, 84 g to birth weights.[7] They estimated that one patient would be prevented from having preeclampsia for every 16 patients treated. Bujold et al, in another publication, added more studies to the above meta-analysis and found a distinct benefit from LDASA in patients with abnormal uterine artery waveforms, particularly in the two studies that included patients who were given the medication at or before 16 weeks.[8] Specifically in this group, significant reductions were noted, with an RR for preeclampsia and severe preeclampsia of 0.48 and 0.38, respectively, in those given LDASA before 16 weeks. In patients with abnormal uterine arteries, five patients would need to be treated for every patient in whom preeclampsia was prevented.

3. Other patients possibly benefiting from LDASA. Space constraints will not allow discussion of all of the screening tests for preeclampsia and IUGR, but the ones that have shown most promise are: first trimester uterine artery waveforms, first trimester placental volume, plasma protein-13 (PP13), second trimester inhibin-A, or combinations of the above.

Who have not yet been shown to benefit from LDASA? Women at low risk for adverse pregnancy outcome or those who have been started on LDASA after 20 weeks.

Is there any danger in giving LDASA? In the second NICHD trial, the incidence of placental abruption was higher in the LDASA group than controls,[2] and this triggered concern about using it for preeclampsia prophylaxis. However, lost in the details of the study was the fact that the difference between abruption in the LDASA group and controls was largely due to an incredibly low rate of abruption in the control group. All subsequent meta-analyses, including the recent Bujold study above, have found no differences between groups in the incidence of abruption or any other complication that might be attributed to the medication.

What seems to be the most efficacious dosage of LDASA? For a while I started prescribing two tablets of

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84 mg a day based on a study showing a greater benefit in preventing strokes in adults using a double dose of "baby" aspirin vs. a single dose per day. However, I soon backed off, realizing this was a simplistic attempt to equate pre-eclampsia in pregnant women to strokes in non-pregnant older adults, and no study has yet pitted a single dose against a double dose for preeclampsia. Interestingly, the Bujold benefit analysis included studies where the dosage varied from 50 mg to 150 mg per day. I suggest staying with a single 84 mg tablet a day.

When should the medication be stopped? This is not going to be answered based on evidence, because none exists. However, in the absence of other factors, we have been stopping LDASA after 34 weeks, simply because some anesthesiologists have been reluctant to give epidurals to patients on LDASA. ■

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Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

45. The use of prayer by patients is supported by:
a. Several large randomized controlled trials
b. People's personal beliefs and faith
c. A large variety of different types of controlled studies
d. All of the above

46. Challenges to interpreting results of prayer studies include:
a. The large number of types of prayer used
b. The different outcomes measured
c. The numbers of participants involved in studies
d. All of the above

47. A physician who wishes to be sensitive to the beliefs and practices of his or her patients should:
a. consider his or her own beliefs.
b. allow the patient time to answer.
c. be prepared to answer questions about his or her beliefs.
d. All of the above

48. SAMe was found to be a safe and effectve add-on therapy to SSRIs for the treating resistant major depressive disorder.
a. True
b. False

Answers: 45. b, 46. d, 47. d, 48. a.

In Future Issues:

Acupuncture and Hot Flushes

Vitamin D and Upper Respiratory Infections

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Dabigatran Leading Race to Replace Warfarin

In this issue: FDA Advisory Committee recommends approval of dabigatran, safety of proton pump inhibitors, effectiveness of glucosamine and chondroitin, FDA Actions.

Advisory Committee recommends approval of dabigatran

In the race to find a drug to replace warfarin, Boehringer Ingelheim may have a leg up with the impending approval of dabigatran. The Cardiovascular and Renal Drugs Advisory Committee of the FDA unanimously recommended approval of the drug in September for the prevention of stroke and systemic clots in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is given in a fixed dose twice a day and does not require monitoring. It is speculated that dabigatran will replace warfarin as the preferred anticoagulant in many settings, including many patients with atrial fibrillation. The approval was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was published last December. The study of more than 18,000 patients with atrial fibrillation showed that dabigatran given at a dose of 110 mg was similar in effectiveness to warfarin in prevention of strokes and systemic embolism, but had a significantly lower rate of major hemorrhage. A higher dose of 150 mg was associated with lower rates of stroke and systemic embolism compared to warfarin and similar rates of hemorrhage (*N Engl J Med* 2009;361:1139-1151). The FDA panel recommended approval of the higher dose, but was split on recommending the 110 mg dose. There was a slightly higher rate of heart attacks with dabigatran compared to warfarin, although the reviewers did not think this was serious enough to warrant holding the drug back. Dabigatran, once approved, will be marketed as Pradaxa®. Several companies are working on their own products to fill the same niche in what has been estimated to be a $10-20 billion market. Drugs in development include Bristol-Myers Squibb's apixaban and rivaroxaban, which is being jointly developed by Bayer Healthcare and Johnson & Johnson. Both drugs are direct inhibitors of Factor Xa. ■

Safety of proton pump inhibitors

Recent studies have suggested that proton pump inhibitors (PPIs) may negate some of the benefit of clopidogrel (Plavix®) in patients with cardiovascular (CV) disease. A new study refutes these findings, and at the same time raises more questions about the safety of PPIs. In a nationwide cohort study from Denmark, all patients discharged after first-time myocardial infarction (MI) were reviewed during 2000-2006. Of the more than 56,000 patients, 16% were rehospitalized for MI or stroke or experienced CV death. Nearly 25,000 patients were discharged on clopidogrel, of which nearly 30% received a concomitant PPI. Patients who were discharged on the combination of a PPI with clopidogrel or on a PPI alone had elevated but similar rates of death or rehospitalization for MI at 30 days (hazard ratio [HR], 1.29 for the combination [95% CI, 1.17-1.42]; HR, 1.29 for PPI alone [CI, 1.21-1.37]), indicating that

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

the risk of a PPI with clopidogrel was no higher than a PPI alone. The authors conclude that there seems to be no significant interaction between PPIs and clopidogrel; however, PPIs may be associated with an increased risk for adverse CV outcomes after discharge. The authors postulate that the increased CV risk from PPIs is likely caused by unmeasured confounders (*Ann Intern Med* 2010;153:378-386). As pointed out in an accompanying editorial, this study may be very confusing for clinicians who have recently received warnings regarding the combination of clopidogrel with a PPI. It further highlights the potential risks of PPIs in patients with questionable or inappropriate indications for the drugs and the need for further studies into their risks and benefits (*Ann Intern Med* 2010;153:413-415). ■

Glucosamine and chondroitin

Millions of patients take glucosamine and chondroitin on a daily basis, hoping it is a safe alternative treatment for osteoarthritis. A new study suggests that the combination is ineffective but harmless. In a meta-analysis of 10 trials and more than 3800 patients, glucosamine, chondroitin, or the combination was compared to placebo with regard to pain scores and X-ray appearance of the hip and knee joint. None of the endpoints crossed the boundary of the minimal clinical important difference (95% credible intervals). The authors conclude that compared with placebo, glucosamine, chondroitin, and the combination do not reduce joint pain or have an impact on narrowing of joint space of the hip or knee. They further state that insurers should not cover the cost of these preparations, but since there is little harm, patients may wish to continue buying and taking it (*BMJ* 2010;341:c4675). ■

FDA Actions

The FDA has announced that it will significantly restrict the use of rosiglitazone (Avandia®) to patients with type 2 diabetes who cannot control the disease on other medications. The FDA had the option of removing the drug from the market, a move that was recently taken by the European Medicines Agency; however, the agency decided to limit access at least for now. Rosiglitazone has been associated with an elevated risk of cardiovascular events.

The FDA has approved fingolimod (Gilenya®), the first oral drug to reduce relapses and delay disability progression in patients with relapsing-remitting multiple sclerosis. The drug is the first of a new class called sphingosine 1 phosphate receptor modulators. Patients need to be closely monitored for symptomatic bradycardia. Fingolimod will be marketed by Novartis Pharmaceuticals.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA has voted against recommending approval of lorcaserin hydrochloride for the treatment of obesity (see September *Pharmacology Watch*). Although the drug was shown to be effective, resulting in at least a 5% body weight loss for half of patients taking the drug over 1 year, there were concerns over valvular heart disease. Arena Pharmaceuticals argued that valvulopathy was not a significant issue and that they met the FDA's predefined goals for safety. The FDA is not required to follow subcommittee recommendations, however it usually does.

The same subcommittee also recently reviewed the weight-loss drug sibutramine (Meridia-Abbott Laboratories) and delivered a **split vote on whether sibutramine should stay on the market.** Sibutramine has been the subject of controversy since last November when initial data from the Sibutramine Cardiovascular Outcomes trial revealed a higher rate of cardiovascular disease associated with the drug. The full study was published in September and showed that cardiovascular events were observed significantly more frequently in the sibutramine group than in the placebo group (11.4% vs 10.0%; $P = 0.02$). The rate of cardiovascular death or death from any cause, however, was no different in the two groups (*N Engl J Med* 2010;363:905-917). The FDA subcommittee voted 8-8, with 8 members voting to remove the drug from the market and the other 8 voting to allow the drug to remain on the market with tougher warnings and a restricted distribution pattern. The FDA vote is expected later this fall.

The **FDA has approved pegloticase for the treatment of refractory gout in patients who have not responded to or can't tolerate conventional therapy.** The drug is administered intravenously every 2 weeks. It appears to work by metabolizing uric acid to allantoin, which is then cleared through the kidneys. The approval was based on two 6-month trials in more than 200 patients that showed the drug reduces uric acid levels and reduces uric acid deposits in joints and soft tissue. About one in four patients will experience severe allergic reactions to the infusion, so patients should be given an antihistamine and a corticosteroid prior to administration. The drug was not studied in patients with congestive heart failure and should not be used in this population. Savient Pharmaceuticals will market pegloticase as Krystexxa™. ■