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Acupuncture for Menopausal Hot Flushes

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MENOPAUSAL HORMONE THERAPY HAS BOTH RISKS AND BENEFITS. THE conclusion of the Women's Health Initiative (WHI) study was that for many women, the risks of menopausal hormone therapy outweigh the benefits.[1] Since that time, many providers and patients have been looking for alternatives to hormone therapy to treat menopausal hot flushes. In 2001, prior to the publication of the WHI study, roughly 70% of women seeking care at a tertiary menopause clinic had used some type of integrative approach to treat their menopausal symptoms, and overall were satisfied with this approach.[2] It is likely that the usage of integrative approaches is even higher today, in the post-WHI era.

Physicians and health care providers, however, may not be adequately educated on integrative approaches to treat menopausal symptoms. An anonymous survey asked family medicine residents and faculty to note whether they were most likely to encourage use, discourage use, or to give no advice on different integrative modalities for various menopausal issues.[3] The majority were most likely to give no advice on acupuncture for vasomotor symptoms, the remainder encouraging (13.4%) or discouraging its use (13.9%) with essentially equal frequency. The authors suggest that physicians are not clear on the advantages or disadvantages of integrative modalities such as acupuncture, bodywork, herbal approaches, and behavioral therapies.

Some of the alternatives to hormone therapy include prescription medications such as venlafaxine, gabapentin, and clonidine. Non-pharmaceutical options that have been studied include Vitamin E, black cohosh, relaxation training, and acupuncture. Acupuncture has been fairly well-studied for menopausal symptoms, although it is one of the modalities that is extremely difficult to study using the gold standard double-blind, placebo-controlled, randomized trial. No one has yet succeeded in either blinding the acupuncturist, or in finding a control that is both valid and inert. That said, acupuncture

Summary Points

- Physicians are not clear on the advantages or disadvantages of nonconventional modalities such as acupuncture, bodywork, herbal approaches, and behavioral therapies.
- The mechanism of action of acupuncture might be related to neurotransmitters.
- When compared with self-care, which likely is not an active control group, acupuncture is statistically better.

trials comparing true acupuncture to sham acupuncture must be thought of as not likely having an inert control intervention.[4,5] A therapeutic effect of the sham intervention would make it harder to demonstrate a difference between real and sham acupuncture.[4]

Mechanism of Action of Acupuncture

What mechanism could explain acupuncture's effects on hot flushes? The exact cause of hot flushes is not known, although thermoregulatory dysfunction is likely involved. Acupuncture, which increases beta-endorphin levels, may affect the sympathetic nervous system via mechanisms at the hypothalamic and brainstem levels.[6] Opioids in the brain seem to stabilize the thermoregulatory center from which hot flushes are initiated.[7] Keeping in mind that the prescription medications used to treat hot flushes each affect the brain, one could postulate that one of the mechanisms of action of acupuncture also might be related to neurotransmitters. In fact, in an animal model, both dopaminergic and serotonergic pathways appear to be activated with electroacupuncture and moxibustion.[8]

Acupuncture Theory of Hot Flushes

Acupuncture for menopausal symptoms aims to correct a condition known as "deficient heat."[9] Yin energy is thought to be deficient in menopause, causing nightsweats and a general mental agitation. Acupuncture points often used in the management of menopausal symptoms balance the kidney chi by subduing kidney yang. Points that nourish the heart and quiet the spirit also are used.[9]

Clinical Trials

The largest controlled clinical trial of acupuncture for menopausal hot flushes is the ACUFLASH study,[10] a multicenter, pragmatic, randomized, controlled trial enrolling symptomatic postmenopausal women. The acupuncture group received 10 acupuncture treatment sessions and advice on self-care, while the control group received advice on self-care only. The primary endpoint was change in mean hot flash frequency from baseline to 12 weeks, and the secondary endpoint was change in health-related quality of life. This study found that hot flush frequency decreased by 5.8 per 24 hours in the acupuncture group (n = 134) and 3.7 per 24 hours in the control group (n = 133), a difference of 2.1, which was statistically significant ($P < 0.001$). Hot flash intensity also decreased significantly. Regarding quality of life, the acupuncture group experienced statistically significant improvements in vasomotor, sleep, and somatic symptoms compared to the control group ($P < 0.001$, $P = 0.002$, and $P = 0.011$, respectively). This study did not have a placebo control, but taken as an effectiveness trial, the results are valid. The observational follow-on study did not show a significant difference between groups at 6 and 12 months,[11] and the authors concluded that acupuncture can contribute to a more rapid reduction in vasomotor symptoms and improvement in health-related quality of life, but that it probably has no long-term effects.

Smaller clinical trials have found similar results. A recent randomized, single-blind study compared shallow needle sham acupuncture (n = 24) to traditional Chinese medicine (TCM) acupuncture (n = 27) in postmenopausal women experiencing hot flushes.[12] Both groups had significant improvements over the 12 weeks of the study, but there were no differences between groups. The investigators note that shallow needling may have therapeutic effects, thus reducing its utility as a "placebo" control.

One study of hot flushes in perimenopausal and postmenopausal women compared three groups: TCM acupuncture, shallow needling, and usual care.[13] All three groups showed an improvement in the frequency of hot flushes across the eight weeks of the study intervention

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($P = 0.01$), but the differences between groups were non-significant. However, the two acupuncture groups showed a significantly greater decrease in hot flushes than the usual care group ($P < 0.05$), but results in the two acupuncture groups did not differ from each other. Because both acupuncture groups were better than usual care, the authors conclude that either there is a strong placebo effect, or that both sham and true acupuncture have clinical effects with respect to reducing hot flush frequency.

In a randomized study, Cohen et al compared menopause-specific acupuncture to general wellness acupuncture in a pilot study.[9] Both were active groups, but the outcome variables included hot flushes, sleep disturbances, and mood changes, all of which were more likely to change with the menopause-specific acupuncture. Hot flush severity and sleep disturbance decreased in the experimental group ($P < 0.05$), but not in the wellness group over the treatment period. Mood changes decreased in both acupuncture groups, which was not surprising ($P = 0.05$). The findings support the use of acupuncture in treating symptoms of menopause in particular, and overall well-being and mood, in general.

Estrogen is known to be effective for hot flushes; thus, it is a reasonable active control group. Forty-five postmenopausal women with vasomotor symptoms were randomized to electro-acupuncture, superficial needle insertion or oral estradiol treatment for 12 weeks, with 6 months' follow-up.[14] The number and severity of flushes were registered daily and the Kupperman index, which is a validated measurement of menopausal symptoms, and a general estimate of climacteric symptoms were completed before, during, and after therapy. In the electro-acupuncture group, the mean number of flushes per 24 hours decreased from 7.3 to 3.5, ($P < 0.001$). Eleven of the 15 women had at least a 50% decrease in number of flushes (with a mean decrease of 82%). Superficial needle insertion decreased the number of flushes per 24 hours from 8.1 to 3.8, also statistically significant ($P < 0.001$). In seven out of 13 women, the number of flushes decreased by at least 50% (mean decrease 83%). In the estrogen group, the number of flushes decreased from 8.4 to 0.8 ($P < 0.001$). The decrease in number of flushes persisted during the 24-week follow-up period in all treatment groups. The investigators conclude that acupuncture is a viable alternative treatment of vasomotor symptoms in postmenopausal women, and that they cannot recommend superficial needle insertion as an inactive control treatment. While estrogen was the most effective treatment, it carries with it risks that some patients will find unacceptable.

Mind-body approaches such as paced respiration and relaxation training also can improve hot flushes; thus, these would be appropriate active controls also. Hormone therapy is contraindicated for women with a history of breast cancer. Breast cancer patients with vasomotor symptoms were randomized to either electroacupuncture or to "applied relaxation," a progressive muscle relaxation technique.[7] Menopausal symptoms and mood were assessed at baseline, during the 12 weeks of therapy, and at 3 and 6 months follow up. In both groups, hot flushes ($P < 0.0001$) and menopausal symptoms ($P < 0.0001$) decreased significantly throughout the course of the study, improvements appearing after 12 weeks of treatment and continuing to the six-month follow-up. Well-being also improved in both groups, but mood improved only in the acupuncture group ($P < 0.05$). The investigators propose that both applied relaxation and electroacupuncture modulate central neurotransmitters, such as beta-endorphin, with secondary positive effects on psychological well-being. A non-controlled pilot study also found that anxiety, depression, somatic, and vasomotor symptoms were improved by acupuncture in breast cancer patients on tamoxifen.[15]

Safety

Acupuncture is safe when it is performed by experienced and well-trained practitioners, using sterile, single-use needles.[4] However, all interventions carry some risk, and acupuncture is no exception. Of 97,733 patients receiving acupuncture, six cases of potentially serious adverse events were reported including exacerbation of depression, asthma attack, hypertensive crisis, vasovagal reaction, and pneumothorax, as noted in a review article.[4] Minor adverse events from acupuncture include bruising, local external bleeding, and needle pain.

Conclusion

The majority of women treated with acupuncture have some reduction in their hot flushes. However, the majority of women treated with sham acupuncture also have a significant reduction in their hot flushes. When compared with other active controls, like estrogen or relaxation techniques, acupuncture shows effectiveness in reducing hot flushes. When compared with self-care, which is likely not an active control group, acupuncture is statistically better. The questions yet to be adequately answered are whether true acupuncture offers more than a placebo effect, and whether sham acupuncture is an active control group. Hot flushes have a high placebo response rate to hormone therapy; placebo treatment caused more than 50% reduction in hot flushes in the clinical trials evaluating oral hormone therapy[4]; it is not surprising that such a placebo response also might be seen in studies of other modalities, including acupuncture.

Acupuncture is generally considered to be a safe procedure, and when comparing it with the known risks of hormone therapy and antidepressants, the risks of adverse

effects with acupuncture are lower. Is it worth a try? This review of the literature suggests there is little to lose by trying acupuncture in the setting of menopausal hot flushes, and potentially much to gain. ■

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PPIs = CAP? The Possible Connection

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Synopsis: *Protein pump inhibitors cause changes in gastric acid that promote bacterial colonization of the upper gastrointestinal tract and may be connected with an extra risk of community-acquired pneumonia, though the research reviewing this effect in humans has been mixed.*

PROTON PUMP INHIBITORS (PPIS) ARE ONE OF THE IMPORTANT tools in the treatment of several upper gastrointestinal conditions, including gastroesophageal reflux disease, gastritis, and peptic ulcer disease. The clinical use of this class of medication varies, from short-term (one to several months) to more chronic use, but they are widely prescribed; PPIs are among the most-prescribed medicine worldwide, accounting for $26.5 billion globally in 2008,[1] and estimates are that approximately 40% of the United States population uses PPIs or H2-blockers (H2Bs).[2] Recently there has been a slew of articles documenting the problems with the continued daily use of PPIs, especially concerning upper respiratory infection (URIs) and community-acquired pneumonia (CAP). This article will review the mechanism of action of PPIs and the proposed association between chronic use and respiratory infections.

Physiology

Both H2Bs and PPIs can increase gastric pH above 4, though PPIs do so more effectively.[1,3,4,5] This pH threshold is necessary to help decrease upper gastrointestinal symptoms, but is also a level above which many bacteria are able to survive when otherwise they would have been

Summary Points

- Numerous articles have documented the problems with the continued daily use of PPIs, especially concerning upper respiratory infection and community-acquired pneumonia.
- Convincing mechanistic data for the effects of PPIs, via increased gastric pH and immune system changes, on bacterial colonization of the upper GI tract and respiratory tract, could translate into an increased risk of respiratory infections, including CAP.

killed by the acidity.[1,3] It is possible that this less-acidic environment allows bacterial colonization of the stomach, and in some cases with bacteria that can colonize the respiratory tract and then cause pneumonia and other respiratory infections.[5,6] For example, people taking PPIs have increased intragastric concentrations of aerobic bacteria, which may also be associated with micro-aspiration and pulmonary colonization.[7] However, sometimes the bacteria found in the stomach of people taking PPIs differ from those collected during bronchoalveolar lavage, leading researchers to postulate that some mechanism other than aspiration may be involved.[7]

In addition, PPIs may cause impaired leukocyte function, including decreased adhesion to endothelial cells and reduced generation of reactive oxygen species involved in bacterial killing.[5]

Retrospective Case-control Research

One of the most common approaches to studying the PPI-CAP connection is via a case-control design. Essentially, cases of CAP in a given demographic are matched with a control group, and then statistical techniques are used to search for variables that most account for why CAP developed in the case group but not in the control group. Allowing the identification of important associations, these research approaches do not, however, pin down a cause-effect relationship; the latter is best left to randomized controlled trials (RCTs). With respect to confounding variables, there are several issues to consider when interpreting the results of the research discussed below. First, some research has found that the recent prescription of PPIs is more highly associated with CAP than distant or long-standing use; perhaps these medicines actually are being used for early, non-specific symptoms of respiratory disease, essentially a misclassification in statistical terms. Also, patients with multiple comorbid conditions may be more likely to be taking PPIs, be older, and be generally more likely to have respiratory infections,[8] so teasing out the effect of PPIs can be difficult.

There were two initial attempts to explore this issue; these studies then formed the basis for a series of follow-up research. In one, researchers examined a large Dutch medical records database for an association between use of H2Bs or PPIs and CAP.[3] A total of 364,683 people who were currently taking or who had recently taken and then stopped PPIs or H2Bs were involved over 2.7 years, and 5,551 cases of pneumonia were identified. Of this group, people currently using either H2Bs or PPIs were more likely to develop pneumonia than people who had stopped using acid-suppressing medication, with adjusted odds ratios (OR) of 1.63 (confidence interval [CI] = 1.07-2.48) and 1.89 (CI = 1.36-2.62), respectively. The researchers noted that the effect of PPIs, but not H2Bs, showed a dose-response effect, making a more convincing case for a true biological effect. As a purely observational research trial, uncontrolled confounders, and misclassification of exposure (prescription of medication was assumed to indicate compliance) and diagnosis (not all pneumonias were confirmed by radiographs) could have compromised results. Another unique, but possibly negative, feature of this trial was that there was no control group not taking any acid-suppressing medication.

Then, a Danish research group examined the demographics and confounding medical illnesses for people discharged from the hospital with a diagnosis of CAP, and matched this group with controls in the general population.[9] The OR of CAP was 1.5 (CI = 1.3-1.7) for people taking PPIs; no association was found for H2Bs (OR = 1.1, CI = 0.8-1.3) nor for people who had taken PPIs in the past. This study was slightly different than the Dutch trial in that it only examined recently hospitalized cases of CAP.

A study in the United Kingdom (UK) was designed to follow up on the previously described studies and address criticisms of confounding variables, and to explain why the greatest risk may have been in recent dosing of acid-suppressing medications vs. people who had been taking the medication for longer periods of time. These researchers used a case-control study in a UK database, selecting 80,066 cases (first diagnosis of CAP during the study period) and 799,881 control patients (from the same general practice site) from a cohort of 7,347,764.[10] Exposure was defined as any PPI use before or after the date of CAP diagnosis. After first analysis, the risk of CAP with PPI use was 2.05 (CI = 1.96-2.15, $P < 0.001$), though this association disappeared after adjusting for all possible covariates, such as comorbid conditions and any of a number of factors that could be associated with an increased risk of pneumonia (i.e., smoking). However, when the results were adjusted for people who had been taking PPIs for less than 30 days (and especially within two days), there was an increased risk of CAP of 1.74 and it remained significant even with covariates factored in (CI = 1.49-2.03; $P < 0.001$). The researchers make a convincing case that their efforts, which included analysis of potentially

significant confounding variables, provided more accurate results than the preceding Dutch and Danish trials that both showed increased CAP risk with PPIs. The researchers also use the fact that there was a more pronounced PPI effect on CAP within a few days of starting the prescription, also seen in the Dutch and Danish trials, as evidence against a causal relationship; it seems more plausible that a "true" biological effect would occur in people who had longer-standing acid suppression and therefore decreased defenses against respiratory bacteria. A secondary analysis looked at risk of CAP with H2Bs and found greater increases in risk, a confusing result given that H2Bs are weaker inhibitors of acid production than are PPIs.

These initial attempts to clarify an association between PPIs and CAP have now been repeated by other research groups focusing on specific demographics. For example, in elderly patients who had survived hospitalization for pneumonia in the past, PPIs increased the risk for recurrent CAP by 12% (OR = 1.5, CI = 1.1-2.1) vs. 8% for non-PPI users, with all of the increased risk accounted for by people who had started PPIs after discharge as compared with those who had been taking PPIs before the original CAP event.[11] Another research group examining 194 cases of CAP in elderly patients in a community hospital failed to find an association with current PPI use, though this study only had categories of use and non-use, whereas most other studies add a third "recent use" category, possibly affecting results.[8] A case-control review of CAP records from 300 general practice clinics in the UK found an adjusted OR of 1.55 (CI = 1.36-1.77) for PPI use within 30 days; there was not an increase in CAP cases with H2B use.[12] As with some of the other trials, there is the possibility of diagnosis misclassification, that the medications weren't actually taken (use was based on prescription), and limitations in diagnostic accuracy (the lack of radiograph confirmation of CAP).

Another trial found an increased risk of recurrent pneumonia in PPI users (RR = 1.16, CI = 1.03-1.31) when compared to nonusers when records from general practices in the UK were examined[13]; this risk only occurred if the PPIs were started within 12 months of the CAP event and there was a small dose-response effect. No increased risk was found for users of H2Bs. The authors postulated that the slightly increased risk demonstrated in this analysis might be due to underlying CAP associated with the GI disorders for which people were being treated with PPIs. Finally, in adults aged 65-94 a CAP case (n = 1,125) control (n = 2,235) study found no increased risk with PPI or H2B use (OR = 1.03, CI = 0.86-1.24), leading the authors to suggest that past positive findings in other trials might be entirely due to confounding variables.[14] These researchers made a significant attempt to follow up on the pneumonia diagnosis to address the misclassification that has plagued other research; it is possible that this enhanced the accuracy of these particular results.

Other Research

There are no PPI clinical trials with respiratory infections as the primary endpoint, so information about this presumed connection has to be gleaned from other types of trials. One meta-analysis of RCTs of PPIs primarily for GERD or PUD provides some initial data regarding the clinical association between PPIs and CAP beyond what we can learn from simple observational studies.[6] The research group located 70 RCTs, only seven of which fit the strict inclusion criteria, mainly because most trials failed to specifically list patients with respiratory infections as adverse effects. Statistical analyses on the seven trials showed a trend toward an increased rate of respiratory infections with PPI use (13%), with five of seven trials demonstrating more infections in the PPI groups than the placebo groups; however, the overall trend was not statistically significant (OR = 1.42, CI = 0.86-2.35, P = 0.17). Of note, one clinical trial in this meta-analysis showed a statistically significant increase in respiratory infections when esomeprazole 40 milligrams daily was administered compared to placebo ($P = 0.05$). The authors of this meta-analysis calculated the number-needed-to-harm as 77; thus, a risk of minimal clinical relevance for the general population.

Another retrospective analysis of the adverse respiratory effects in 31 RCTs (16,583 patients total) of esomeprazole at 20 or 40 milligrams daily vs. placebo or other PPIs (lanzopresole or omeprazole) found no significant difference in the rate of respiratory infections, including pneumonia, in patients with gastric acid-related disorders.[15] With this type of study, there is a possible selection bias as a result of only including patients with specific medical conditions, in this case, gastric acid-related disorders.

Hospital-acquired Pneumonia

There is a significant body of information suggesting an association between H2Bs and pneumonia in the critical care setting,[6] although some trials have either shown no connection[7] or simply a non-statistically significant trend. One example is a cohort of 63,878 patients admitted to the hospital, excluding the intensive care unit, where PPI, but not H2B, use was associated with an increase in hospital acquired pneumonia (OR = 1.3, CI = 1.1-1.4).[16] Sedatives and neuromuscular blockers, but not PPIs, were associated with an increased risk of pneumonia in 787 patients in the medical intensive care unit.[17]

Summary

PPI are a widely prescribed class of medications for a variety of gastrointestinal disorders. There are convincing mechanistic data for the effects of PPIs, via increased

gastric pH and immune system changes, on bacterial colonization of the upper gastrointestinal tract and respiratory tract, which could translate into an increased risk of respiratory infections, including CAP. Most of the clinical research on PPIs and CAP risk comes in the form of either case-control research or retrospective analyses of adverse effects that occurred with the use of PPIs in RCTs on gastrointestinal disorders. In the former, results have been mixed, with some analyses showing a connection between PPI use (current, more than past) and CAP, with others showing no effect. In some cases, a dose-response effect was documented, and usually, but not always, the PPI effect was greater than that for H2Bs. Differing results could be due to variations in demographics (country, age, comorbidities, etc.) or research methodologies (the type of controls, identification of confounding variables, documentation of medication compliance or radiographically-confirmed CAP). Interestingly, some studies have shown an increased CAP risk with recently prescribed PPIs, a bit counterintuitive; different researchers, as explained above, have offered explanations for why this might have occurred or what it might mean. The second type of research methodology, a secondary retrospective analysis of adverse effects in trials using PPIs for gastrointestinal disorders, has failed to find a PPI-CAP connection. Most researchers addressing this topic, even when study results were negative, mention the importance of factoring in a possible respiratory connection with PPI use; the morbidity and mortality associated with CAP is not negligible, making it extremely important to be prescribing PPIs for only established indications.

Recommendation

Until the medical research completely resolves any possible PPI-CAP connection, it seems prudent to judiciously apply a risk-benefit analysis to a given patient's situation when making a decision to start or continue PPIs. The medical literature hints at a slightly higher CAP risk for people who have recently started PPIs, for elderly patients who previously had CAP and then started PPIs, and generally with PPIs employed at the higher end of their dose range. Extra care is, of course, warranted in considering these medications in people for whom CAP would be particularly devastating, such as the elderly. One researcher said it well: "…there is good evidence that (PPIs) are frequently being prescribed for non-specific and inappropriate reasons, and that a large number of patients are taking these agents for much longer than necessary…stop these agents in patients with previous dyspepsia but no endoscopic disease or gastric irritant use…(r)educe dose gradually over a period of a few weeks to avoid rebound acid secretion…"[1] With this approach, clinicians would avoid some of the possible CAP risk with the use of PPIs. ■

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It Takes Two: Homeopathy and Rheumatoid Arthritis

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Source: Brien S, Lachance L, Prescott P, et al. Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: A randomized controlled clinical trial. *Rheumatology* November 2010. Doi:10.1093/rheumatology/keq234

Synopsis: *Results of this unique randomized controlled trial of homeopathy for people with active rheumatoid arthritis (RA) suggest that any therapeutic benefits that might occur are due not to the specific remedy employed but to the empathetic and healing nature of the homeopathic process of consultation. The question begging to be asked is, what can any practitioner take away from this conclusion?*

The majority of conventional medical practitioners look askance at the practice of homeopathy. They are also, however, challenged by the existence of a small but significant number of methodologically sounds studies reporting therapeutic benefits with homeopathy in select clinical settings. One of those settings is RA. The authors of this exploratory multicenter, double-blind, randomized, placebo-controlled clinical trial sought to tease out which aspects of homeopathy could be of adjunctive benefit to patients with active RA who also were receiving conventional medical therapy.

Adult subjects with active RA were recruited from three British outpatient rheumatology clinics. Patients were screened at baseline and then randomized. The researchers used a 5-arm design where patients receiving a consultation randomly were prescribed individualized (classical) homeopathy, a fixed combination of remedies (also called complex homeopathy, where remedies for specific maladies are offered without homeopathic consultation), or placebo. Those not receiving the consultation received either complex homeopathy or placebo. The study authors posit that their design permits comparisons between consultation and non-consultative treatment, and the effects of complex treatment, individualized treatment or placebo.

Subjects who were randomized to consultation had a meeting with one of two experienced and classically trained homeopaths from visits 2-6 inclusive (initial consultation lasted for one hour; all follow-ups were 30 minutes long). Individualized homeopathic treatment was prescribed at each visit as would normally occur in the practitioners' practices. Subjects received their trial medications via mail from an off-site homeopathic pharmacist. Remedies were either individualized homeopathic remedies in the form of tablets, prescribed from the entire homeopathic repertoire and all at ultra-molecular doses as determined at post-analysis review; or a standardized commercial homeopathic complex previously reported as efficacious for RA. Patients and study staff were aware of consultation allocation but blinded to treatment allocation.

The content of the consultation process was partially standardized—specific topics were always covered (detailed clinical history, current symptoms and medication, assessment of emotional and mental states, etc.). In between clinic visits, patients completed weekly diaries recording pain, global assessment, and adverse events.

Primary outcome measures of interest were: 1) the proportion of subjects meeting the ACR (American College of Rheumatology) 20 improvement criteria, and 2) improvement in the subjects' global assessment of health. Secondary outcomes included DAS (Disease Activity Score)-28 measures of change in disease activity over time and changes in mood as assessed by an affect scale, among others. Participants also completed questionnaires regarding expectations of outcome, a sense of coherence scale to assess the degree to which subjects felt their lives made sense, and tools measuring degree of spirituality and beliefs about integrative therapies.

Participants were withdrawn from the study if their disease-modifying antirheumatic drugs (DMARDs) were changed or if they received > 80 mg steroids total during the treatment period. Intention-to-treat analysis was employed.

A total of 83 subjects were randomized, 6 of whom dropped out before treatment, leaving data from 77 subjects for final analysis. No significant differences were identified between the effects of consultation or treatment allocation for the primary outcomes of ACR20 and improvement in global assessment. Adverse effects did not differ significantly between the groups, and measures of treatment expectations, coping style, spirituality, sense of coherence, and other like variables did not predict outcome for the primary variables.

Regarding secondary outcomes, however, receiving a

homeopathic consultation was associated with a significant improvement over time in DAS-28 compared with no consultation (mean group difference of 0.623, 95% confidence interval [CI] 0.186-1.06, $P = 0.005$). Receiving homeopathic consultation also was associated with a significant reduction in the number of swollen joints (group difference of 3.04, 95% CI 1.055-5.030, $P = 0.0030$) and current pain (group difference 9.12, 95% CI 0.521-17.718, $P = 0.038$) compared with those not experiencing homeopathic consultation. Further analyses showed that receiving a homeopathic consultation significantly reduced weekly pain compared with no consultation, and that subjects receiving placebo compared with individualized homeopathic remedies reported significantly improved patient global health assessment. No significant differences were detected regarding homeopathic treatment allocation.

The authors conclude that homeopathic intervention in people with active but relatively stable RA offers significant clinical benefits attributable primarily to the homeopathic consultation process, and not to the homeopathic remedies themselves.

■ COMMENTARY

RA is a chronic inflammatory disease that can significantly impair quality of life and overall health status. While DMARDs are commonly used to treat the disorder, they are not always effective and carry the potential for significant side effects. As is the case with many chronic ailments, the medical community's search for safe and effective measures to slow, if not altogether stop, underlying pathophysiologic processes continues with great hope for future treatments, while present-day patients often turn to CAM therapies in an attempt to gain added control over their health circumstances. Homeopathy is one therapy that many people, especially Europeans, turn to in confidence. That rosy outlook is not often shared by conventional health practitioners, in large part because explanations for the activity of homeopathic remedies run counter to widely accepted science.

The current study suggests that when therapeutic benefit can be ascribed to a homeopathic approach to RA treatment its source is not the remedy, regardless of how it was chosen, but the relationship engendered between practitioner and patient by the homeopathic consultation, a whole person evaluation that is necessarily individualized, in-depth, and collaborative. This is deemed a mere placebo effect.

The authors review the published data supporting a role for homeopathic remedies in the context of RA, be they individualized or complex in nature, and are to be congratulated for their creative and pragmatic use of a multicenter randomized clinical trial to assess qualitative issues over an extended period of time. Yes, the sample size was relatively small, but methodologically the study is strong. It is not methodology that weakens the results of this paper. It is their interpretation.

To restate, the author's conclude that the benefits of homeopathy, when present, are primarily due to the development of a healing relationship between patient and practitioner that involves trust, empathy, and hopefulness. Rather than an indictment of homeopathic remedies, this statement could more correctly be taken as an indictment of the conventional medical consultation process that often lacks these same interpersonal characteristics. Nowhere is the contrast between approaches mentioned, only the conclusion that homeopathic remedies are likely inactive in the setting of RA.

Regardless of one's bias regarding the potential for clinical benefit from homeopathy, and bias seems inherent in any discussion of homeopathy, almost all health care practitioners believe in the power of relationship. To point out that the empathic nature of a homeopathic consultation may be the source of clinical improvement, without acknowledging that the harried nature of conventional medical practice today does not allow for the consistent development of healing relationships, misses the forest for the trees. Do homeopathic remedies work for people with RA? These results suggest no. Is a healing relationship the foundation of an effective medical encounter? Yes. If it takes a "negative" homeopathic trial to reinforce that belief, *Alternative Medicine Alert* will review more such studies. ■

Turning Red: Variability in RYR Products

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Source: Gordon RY, Cooperman T, Obermeyer W, Becker DJ. Marked variability of monacolin levels in commercial red yeast rice products. *Arch Intern Med* 2010;170:1722-1727.

Synopsis: *A mixture of monacolins is the primary candidate for the active participle of red yeast rice, (RYR) an over-the-counter remedy frequently used to help control elevated cholesterol levels. This study reveals wide variations in the monacolin content of a sample of red yeast products that may significantly impact therapeutic response, as well as the presence in some of potentially toxic contaminants.*

The authors behind this investigation determined monacolin levels in a sample of 12 commercial RYR formulations and tested for the presence of citrinin (CN), a mycotoxin known to cause renal damage in animals. Twelve commercial RYR products, which the authors state were representative of commonly sold formulations available in the United States, were purchased and sent for analysis by an independent testing organization. Products were bought online from retailers, catalogs, multilevel marketing companies, or directly from the manufacturer. Two of the formulations had been tested earlier in association with their use in clinical trials. The remaining 10 products were tested in 2008 as part of a product review of RYR supplements published by the online subscription service ConsumerLab.com. A single lot for each product was tested for content of specific monacolins, disintegration, and for contaminants, specifically CN and lead.

Results showed significant variability between the various products with respect to total monacolin content, monacolin K (MK, frequently referred to as lovastatin), and the hydroxy form of MK. Four of the 12 products contained elevated levels of CN. None of the products, however, contained lead in excess of contamination limits, and all were found to disintegrate properly.

The authors conclude that dramatic variation exists between RYR products and their content of potentially active ingredients. In addition, a significant number of RYR products on the market have the potential to harm people taking them due to the presence of CN.

■ COMMENTARY

RYR has been used in Asia for centuries as a medicinal agent and food colorant, and is produced by culturing the yeast *Monascus purpureus* on rice. The process creates monacolins, a group of compounds that inhibit hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme you will likely recognize as the conventional prime target for the therapeutic reduction of hepatic cholesterol synthesis. Monacolin K, or MK, is marketed as lovastatin; therein lies a significant rub, as the Food and Drug Administration (FDA) typically considers RYR a dietary supplement, but when the monacolin content of RYR is standardized it may be considered a drug. Such was the genesis of FDA action against a number of companies selling RYR in recent years.

RYR remains on the shelves of many pharmacies and health food stores, and it is easily obtained over the Internet. Interest in its use among the population with high cholesterol has soared. Studies suggest that well-formulated RYR products can effectively lower cholesterol levels, and apparently with somewhat lower risk for liver and muscle dysfunction than statin drugs. Research results point to RYR also being a viable option for people with high cholesterol who are intolerant of statin therapy.[1] (See review in the September 2009 issue of *Alternative Medicine Alert.*)

But the results of this paper suggest a real problem—the lack of standardization of monacolin content across products. In fact, there having been only one lot tested from each manufacturer, it is possible that batch-to-batch variability also exists in this regard. On the other hand, as the authors note, the majority of the work done for this investigation took place before many companies phased in the Good Manufacturing Practices (GMPs) recently mandated for supplement manufacturers. The question of the presence of CN in some products raises another red flag that hopefully has been addressed through the GMPs, but we cannot yet know this for certain.

The precautionary tale woven throughout this article is not without its own shortcomings. For example, the authors state the products chosen were representative of those widely available in the marketplace but we are left to take their word for that, even though no products were purchased directly off store shelves. Nor do we know why the specific number (12) of products was chosen. To the authors' credit, they point out another limitation of their investigation is that it remains unknown whether there might be active ingredients apart from monacolins in RYR products.

Although the supplement industry seems to be cleaning up its act, there is still reason for a "buyer beware" mentality, as evidenced by the data presented here. Should a person be using RYR and not experience a significant therapeutic response, the knee-jerk reaction might be that RYR is not effective, when in fact the product may not contain sufficient active ingredients. Wherever possible, it is important to point our patients in the direction of companies who adhere to the GMPs now in place to best ensure safety and clinical effectiveness for any and all supplement use. ■

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Skim Milk Gets a Move On

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

Dr. Wilke is Chair, Department of Integrative Medicine, Ross University School of Medicine, Commonwealth of Dominica; he reports no financial relationship to this field of study.

This article originally appeared in the November 15, 2010, issue of Internal Medicine Alert. *At that time it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *Three 8-oz glasses of fat-free milk per day provided significant relief to patients with functional constipation.*

Source: Aydin S, et al. Fat-free milk as a therapeutic approach for constipation and the effect on serum motilin and ghrelin levels. *Nutrition* 2010;26:981-985.

These investigators from Turkey hypothesized that fat-free milk could improve constipation and that the hormones motilin and ghrelin are involved. Ghrelin, a "hunger" hormone produced in the stomach and pancreas, stimulates appetite. It has several other effects on the gastrointestinal (GI) tract, but for this study, its enhancement of motility was the effect of interest. Motilin is secreted in the small intestines and stimulates gastric motility and small intestinal peristalsis.

Thirty (30) constipated patients and 19 controls were recruited. All subjects underwent double-contrast barium enemas. Exclusion criteria included pre-existing GI pathology (cancer, lactose intolerance, ulcerative colitis, Crohn's disease, malabsorption syndrome, among others), and other disease or conditions associated with constipation (diabetes, thyroid disease, pregnancy, obesity, and tobacco use). The constipated subjects were classified by the Constipation Severity Instrument (CSI), a validated tool for accessing constipated patients,[1] into three groups, mild, moderate, and severe, with 10 subjects in each group. The CSI for the mild group averaged 17.8, for the moderate group 20.2, and for the severe group 26.7. The controls were divided into two groups with CSIs of 10 and 9. All groups were evenly divided between men and women with average body mass indices around 26 kg/m^2. The groups were well matched, except that the constipated patients ate fewer legumes, whole grains, and fresh fruits and vegetables. Milk consumption among the constipated patients was limited to 1-2 glasses of whole milk per week. None of them consumed fat-free milk.

Blood samples for electrolytes, lipids, ghrelin, and motilin were obtained at baseline and then after 3 days of fat-free milk consumption. All subjects were given a standard diet (45% carbohydrates, 35% fat, and 20% protein).

CME Instructions

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

1. Which of the following is TRUE regarding PPIs and community-acquired pneumonia?
   a. Per the medical literature, the people most at risk for CAP are those who have been taking PPIs for a long period of time versus those who just recently began PPIs.
   b. When individual PPIs were analyzed, esomeprazole seems to carry with it the greatest CAP risk.
   c. There are numerous RCTs examining PPI use and its direct effect on CAP from which conclusions about this topic can be drawn.
   d. H2Bs seem more associated with a higher CAP risk than PPIs.

2. Which of the following is not a minor adverse risk associated with acupuncture?
   a. Needle pain
   b. Pneumothorax
   c. Bruising
   d. Local bleeding

3. Acupuncture is equally as effective as estrogen therapy in treating hot flushes.
   a. True
   b. False

4. Which of the following physical and biochemical changes was reported by constipated subjects who drank fat-free milk?
   a. A decrease in the Constipation Severity Index
   b. An increase in weight
   c. A decrease in serum ghrelin
   d. An increase in serum calcium
   e. An increase in bone mass

Answers: 1. b, 2. b, 3. b, 4. a.

The subjects in control group 1 (CG1) drank 400 mL of fat-free milk a day; those in control group 2 (CG2) drank the same amount of whole milk. The mild, moderate, and severe constipation cases received 400, 600, and 800 mL of fat-free milk, respectively, a day for 3 days.

CG1, which drank fat-free milk, saw an increase in ghrelin levels and a 3-point drop in CSI, while those subjects in CG2, who drank whole milk, saw a decrease in ghrelin and a 1-point drop in CSI. Motilin levels did not change significantly in CG1, but fell in CG2. Similar results were seen in the constipated groups, which all drank fat-free milk. In the mild group, the CSI fell 4 points, 12 points in the moderate group, and 17 points in the severe group. In fact, the post-fat-free milk CSIs in the moderate and severe groups were equal to the control groups. Ghrelin levels rose in all constipated groups. In contrast to CG1, however, motilin levels also rose.

Samples of the whole and fat-free milk were analyzed for chemical content. The only significant differences were the amount of iron (twice as much in whole milk than in fat-free milk) and the amount of ghrelin (more in fat-free milk than in whole milk). Motilin concentrations were equivalent.

■ COMMENTARY

This study was poorly written and confusing to follow. It was not a double-blinded, randomized, placebo-controlled study. It was not clear when the CSI was repeated, 3 or 30 days after baseline. The results need to be replicated in another environment with a larger and more ethnically diverse group of subjects and a study design that minimizes bias. Even with that, the results are interesting and raise several questions. Why is the concentration of iron higher in whole milk and does that matter for this study? Primary care physicians often receive anecdotal reports of constipation with iron supplementation, and research supports this observation in pregnancy.[2] How much milk does one need to drink? For constipation, the magic number seems to be 600-800 mL (20-27 fluid oz) of fat-free milk a day. What would the effect of a similar volume of 1% or 2% milk be? These volumes of milk would cause symptoms in lactose-intolerant individuals. Would constipated, lactose-intolerant patients benefit from taking lactase before consuming fat-free milk or by drinking lactase-treated fat-free milk? What about fat-free fermented milk? How do we account for the increase in ghrelin and motilin serum values in subjects given fat-free milk? While it's safe to assume that the motilin increase represents endogenous production, since there is no significant difference between fat-free milk and whole milk in motilin concentration, the same cannot be said for ghrelin.

These subjects almost certainly had functional constipation, which is defined by the Rome III criteria as the presence of two or more of the following symptoms occurring for at least 12 weeks in the preceding 12 months: 1) straining during at least 25% of defecations; 2) lumpy or hard stool in at least 25% of defecations; 3) a sensation of incomplete evacuation in at least 25% of defecations; 4) a sensation of anorectal obstruction or blockage in at least 25% of defecations; 5) manual maneuvers to facilitate defecation used in at least 25% of defecations; and 6) fewer than three bowel movements in a week.[3]

Constipation has many causes. As a society, we aren't physically active, and we don't keep ourselves adequately hydrated. Our consumption of fat-free (skim) milk, whole grains, and fruit and veggies is low. Some constipation is iatrogenic from narcotics and medications with anticholinergic side effects. Sometimes constipation is a red flag for a more serious disease. When a patient presents with this complaint, we need to look at lifestyle issues and medication lists and search for GI pathology. Laboratory tests include thyroid-stimulating hormone (TSH), serum calcium, glucose, electrolytes, a complete blood count, and urinalysis.[4] Advocating fat-free milk seems like a very reasonable approach, if the constipation is functional and the patient is not currently drinking it, especially since milk consumption has other benefits. For patients who complain that they don't like the taste of skim milk, suggest that they "wean" themselves off milk with higher fat concentrations gradually. Going from whole milk to 2% to 1% to skim, one bottle at a time, is doable. ■

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In Future Issues:

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CoQ10 for Heart Disease
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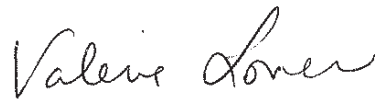

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