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CAM for Fibromyalgia — A Summary of Evidence

By Nancy J. Selfridge, MD

Dr. Selfridge is Associate Professor, Department of Integrated Medical Education, Ross University School of Medicine, Commonwealth of Dominica, West Indies; she reports no financial relationship to this field of study.

Introduction

FIBROMYALGIA (FM) CONTINUES TO PRESENT MANAGEMENT CHALLENGES for patients and their physicians despite a number of new pharmaceuticals promoted for its treatment. The original diagnostic criteria published by Wolfe et al in 1990 formed the basis for patient inclusion in most extant research on FM. These criteria include the presence of chronic widespread pain of at least 3 months' duration and the presence on physical examination of at least 11 out of 18 possible tender points.[1] Wolfe recently proposed a new set of criteria for the disorder that allow for better categorization of the disease and its debilitating symptoms. Chronic widespread pain for at least 3 months' duration remains a hallmark in these new criteria. However, the consensus is that the number of tender points is no longer relevant. Instead, a Widespread Pain Index is used to document painful areas and a Symptom Severity Scale Score is used to assess the severity of associated symptoms such as fatigue, cognitive difficulties, and waking unrefreshed.[2] (*See Table.*) It is interesting to note that when the criterion for tender points is eliminated, the marked female predominance of the disorder is reduced.[3]

FM Pathophysiology

FM has long been considered an idiopathic entity and it has been argued that it does not even represent a separate clinical disorder. The result of this debate has been that physicians have treated many patients with significant symptoms dismissively, a stance that potentially is harmful and no longer is tenable. Increasing research evidence supports the hypothesis that the pathophysiology of FM is the result of genetic and biologic factors, environmental triggers, and neurophysiologic abnormalities. Functional magnetic imaging studies provide direct evidence of increased central pain sensitivity

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and it generally is agreed that this is the result of both central augmentation of sensory input and diminished central pain inhibitory function.[4,5] It has been hypothesized that stressful triggers — such as an accident, a flulike illness, emotional stress, or overwork — that precede the onset of symptoms in many patients may be part of the pathophysiology of central pain sensitization.[6] Though the precise role of environment and stress in the pathophysiology of FM is not yet elucidated, they should not be downplayed in the clinical setting. The opportunity to express and think about stressful triggers may provide patients with valuable insights.

Autonomic dysfunction is present in FM patients, explaining a number of patient complaints including worsening of symptoms with stress. Several neuroendocrine and immune function alterations have been documented including elevated cerebrospinal fluid levels of substance P, abnormalities in the regulation of cortisol, abnormalities in adrenergic and serotonin systems, and diminished growth hormone secretion with increased levels of proinflammatory cytokines in response to exercise.[7,8] Though such alterations may not play a role in the etiology of the FM, they may contribute to persistence of symptoms. Comorbid depression is common in FM and worsens both symptom severity and prognosis. Thus, careful screening for depression and treatment for it when present should be pursued aggressively.

CAM for FM

Current conventional treatment strategies often include recommendations for prescribed medications, exercise, and physical and psychological therapies. Few FM patients achieve high levels of symptom relief even with this multidisciplinary approach. Thus, many patients seek complementary or alternative medicine (CAM) treatment. CAM is defined as a diverse set of diagnostic, treatment, and preventive practices based on philosophies and techniques other than those used in conventional allopathic Western medicine. "Alternative" refers to practices used in place of conventional medicine, whereas "complementary" refers to practices that are used along with conventional medical treatment. Many conventionally trained physicians who use CAM prefer to describe their practices as "integrative": using the best interventions from all practices, tailored to the needs and preferences of each individual patient, and having the greatest potential for good and the least potential for harm. For the sake of this article, CAM will be used to describe interventions that have not been considered part of conventional Western medicine. A Mayo Clinic survey of FM patients referred to a tertiary care program reported 98% had used some form of CAM within the preceding 6 months.[9]

Evaluating the efficacy of various CAM therapies often is challenging. Though randomized controlled trials (RCT) are considered the strongest research basis for clinical recommendations, many CAM therapies focus on an individualized patient approach as part of the healing process. Thus, standardization of the therapy and blinding of the patient and the practitioner may be impossible in an optimal therapeutic setting. Still, some evidence-based support exists for certain CAM therapies in the treatment of FM.

Nutrition and Supplements

An RCT comparing a 6-week course of vegetarian diet to amitriptyline demonstrated some pain reduction in the diet group compared to baseline, but more overall improvement in the amitriptyline group.[10] Evidence of efficacy for most supplements and botanicals is lacking, though patients often try various natural medicines in their quest for help. Topical 0.025% capsaicin cream applied to tender points was shown to reduce FM pain after 4 weeks in one double-blind study of 45 patients. Topical capsaicin cream often causes a burning sensation on initial application, which can be problematic for patients already quite sensitive to pain stimuli.[11] Although St. John's wort may be effective for depression and is often tried by FM patients based on its purported effects on neurotransmitter levels, it has not been studied specifically for FM. Further, it is a potent inducer of cytochrome P450 and can reduce the effectiveness of many drugs, including oral contraceptives. Patients considering its use should be counseled about its lack of proven benefit and the potential for drug interactions. Oral SAMe (S-adenosylmethionine) may

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Table: Fibromyalgia Diagnostic Criteria

Criteria

A patient satisfies diagnostic criteria for fibromyalgia (FM) if the following 3 conditions are met:

1) Widespread pain index (WPI) ≥ 7 and symptoms severity (SS) score ≥ 5 or WPI between 3-6 and SS scale score ≥ 9.
2) Symptoms have been present at a similar level for at least 3 months.
3) The patient does not have a disorder that would otherwise explain the pain.

Ascertainment

1) WPI: note the number of areas in which the patient has had pain over the last week. Score will be between 0-19.

Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Neck
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Upper
Upper arm, left	Upper leg, left	Chest	Lower back
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		

2) SS scale score:

Fatigue

Waking unrefreshed

Cognitive symptoms

For each of these 3 symptoms, indicate the level of severity over the past week using the following scale:

0 = no problem

1 = slight or mild problems, generally mild or intermittent

2 = moderate, considerable problems, often present and/or at a moderate level

3 = severe; pervasive, continuous, life-disturbing problems

Also, rate somatic symptoms in general using the following scale:

0 = no symptoms

1 = few symptoms

2 = a moderate number of symptoms

3 = a great deal of symptoms

SS scale score is the sum of the severity of fatigue, waking unrefreshed and cognitive symptoms PLUS the extent of somatic symptoms in general. Final score will be between 0-12.

*Somatic symptoms may include but are not limited to: muscle pain, irritable bowel syndrome, muscle weakness, headache, pain/cramps in abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, nausea, nervousness, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, shortness of breath, Raynaud's phenomenon, hives/welts/rashes, tinnitus, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, loss of appetite, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, bladder spasms

Adapted from: Wolfe F, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptoms severity. *Arthritis Care & Research* 2010;62:600-610.

have beneficial effects for FM patients. A double-blind, controlled crossover study of 17 patients showed improvement in number of painful sites ($P < 0.02$) and in depression scores ($P < 0.05$) with SAMe treatment but not with placebo.[12] In a 6-week double-blind, placebo-controlled study of 44 patients taking SAMe at 800 mg daily, the greatest improvements occurred for pain ($P = 0.002$) and for mood ($P = 0.006$) for the treatment group compared to controls.[13] Oral SAMe at this dose is considered generally well tolerated, but it can be expensive. Valerian, passionflower, chamomile, and melatonin often are used to help with the sleep disturbance common in FM patients. All of these substances may have some sedative or sleep-inducing qualities but none have been studied for effectiveness in FM patients. A proprietary combination of magnesium and malic acid (Super Malic) was shown effective in a single randomized, blinded, controlled pilot study of 24 patients, but only at a dose of 6 tablets daily.[14] Magnesium and malic acid have not been studied alone. 5-HTP showed promise in an open 90-day study of 50 patients with significant improvement in all clinical variables compared to baseline measures ($P < 0.001$).[15] Cases

of eosinophila myalgia syndrome associated with the use of 5-HTP were traced to a contaminated synthetic L-tryptophan from a single manufacturer. There have been no definitive cases of toxicity linked to 5-HTP use worldwide in the last 20 years. Combining the use of 5-HTP with serotonergic antidepressants may increase the risk of serotonin syndrome.[16,17]

Exercise

A 2008 systematic review concluded that aerobic exercise has a beneficial effect on improving physical function and decreasing some symptoms in FM patients.[18] It is not uncommon for exercise to cause an increase in FM symptoms initially, and adherence and attrition have been a problem in research studies on exercise for FM. Tai chi, yoga, and cumulative daily 30 minutes of self-selected lifestyle physical activity were reported to be beneficial for some FM symptoms in recent small trials and may be associated with less exacerbation of symptoms on initiation of the activity.[19-21]

Acupuncture

A recent qualitative review concluded that acupuncture may be helpful for FM and highlighted the different study designs that hinder comparisons and conclusions.[22] Some studies have used standardized acupuncture treatment protocols and others have used individualized treatments deemed more appropriate for the heterogeneity of symptoms presented by FM patients. Sham treatments, both insertive and non-insertive, have been used as placebo-control treatments, but it has been postulated that any kind of needling may produce a nonspecific effect on FM symptoms. Any final conclusions about acupuncture effectiveness for FM will have to wait for more high-quality RCTs with comparable designs and long-term follow-up.

Mind-Body Interventions

Mindfulness meditation may be helpful for depression associated with FM, though a recent randomized, three-armed controlled study showed no beneficial effect of meditation training for FM.[23,24] In this study, the authors concluded that the design, which included significantly long and intrusive data collection periods, may have created enough of a burden for patients that any benefits of the meditation intervention were negated. A recent RCT of 42 patients using an "Affective Self Awareness" program, consisting of a group intervention including emotional disclosure journaling, meditation, and education about mind and body interactions, showed significant benefit for both FM pain symptoms ($P < 0.001$) and perceived level of function ($P < 0.001$) compared to a wait list control group.[25]

Other Therapies

A recent systematic review of RCTs evaluating various CAM therapies for fibromyalgia found some promise for a variety of interventions. Balneotherapy is the use of thermal and mineral baths traditionally offered in various parts of the Middle East and Europe to treat pain and rheumatic disease. The authors of this review concluded that balneotherapy for FM is likely beneficial based on four RCTs, even though the studies varied in the constitution of the mineral baths, the therapy settings, and the control group treatments. One high-quality randomized, placebo-controlled, double-blind trial of individualized homeopathy (n = 62) resulted in significant improvements in pain and quality of life measures in the treatment group. An RCT testing the effects of massage vs. both wait-list and education control groups in 52 subjects showed improvements in pain and Fibromyalgia Impact Questionnaire results in the massage group vs controls, but 90% of the pain-relieving effect was gone at 6-month post-study follow-up.[22]

Conclusion

To date, studies assessing the efficacy of CAM interventions for the treatment of FM have been fraught with methodological flaws. The few higher quality RCTs that exist for any given therapy vary in design, tend to be small studies, and lack long-term follow-up to assess for sustained improvements. Presently, there appears to be some evidence to support exercise, acupuncture, certain mind-body interventions, massage, homeopathy, and balneotherapy as potentially helpful treatments for FM symptoms. There also is some evidence to support the use of topical capsaicin, 5-HTP, and SAMe for FM. More high-quality, large RCTs addressing previous methodological problems need to be done before firm conclusions can be drawn about CAM therapies and their efficacy in the setting of fibromyalgia.

Recommendations

As a very heterogeneous group of patients, FM sufferers deserve treatment individually tailored to their symptoms and preferences, and the therapeutic benefit of generous listening from their doctors. Many will want to explore CAM therapies to use alone or as an adjunct to prescribed medications for FM and will benefit from their physicians' support and guidance. Exercise can be strongly recommended as helpful. Though patients may experience some increased pain with initiation of an exercise program and will need to be supported through this, those who can persist are likely to reap benefits. Patients may wish to explore tai chi and yoga as exercise modalities. A trial of acupuncture would be rational based on current evidence. Massage, homeopathy, and balneotherapy,

and the prudent use of some dietary supplements, can be recommended, though strong evidence of efficacy is still lacking. Meditation training and practice can be suggested and endorsed. When patients are open to the notion of a mind-body connection or note that stress and emotions worsen their symptoms, they may benefit from a formal or informal program of education and emotional disclosure journaling. These CAM therapies are all low risk, except for cost. When patients wish to try natural medicines and supplements, they need to be counseled about potential side effects and interactions with other supplements and prescribed medications. ■

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'Aspirin-like' Botanicals: Are They a Clinically Adequate Substitute?

By David Kiefer, MD

Dr. Kiefer is Clinical Instructor, Family Medicine, University of Washington, Seattle; Clinical Assistant Professor of Medicine, University of Arizona, Tucson; and Adjunct Faculty, Bastyr University, Seattle; he reports no financial relationships relevant to this field of study.

The story behind acetylsalicylic acid (ASA), also known as aspirin, is a fascinating one, both from its botanical origins and its modern recommendations. A classic pain-killer and antipyretic, ASA also is being recommended as primary and secondary prevention for people with diabetes, hypertension, stroke, and coronary artery disease, and is relatively innocuous, barring the small increased risk of gastrointestinal and other bleeding events. Nonetheless, patients still ask for "natural" blood thinning or pain-relieving alternatives. Presumably, many of you in clinic have heard, "Can I take herb X instead of aspirin, please?" or "Will you help me to wean off of warfarin or aspirin?" Below is a discussion of the botanical underpinnings of ASA, that is, plants with related compounds and relevant clinical evidence (referred to below as "aspirin-like" botanicals, or ALB), as well as a brief review of the current recommendations for ASA itself. Essentially, in what situations should clinicians be prescribing ASA or, alternatively, one of its botanical counterparts?

History

The history of ASA as a purified medicinal compound is relatively recent, hailing from the 19th century. However, the medicinal use of its botanical precursors predates the pharmaceutical by hundreds of years. There is some mention of willow (Genus *Salix*), perhaps the most well-known ALB, in the Ebers papyrus from 1534 B.C.[1] Various species of willow commonly grew in the ancient world, and descriptions in the Ebers papyrus document the use of willow for aches and pains and, interestingly, as a general tonic.

The modern history of ASA probably can be said to begin with the purification of the active compound, called salicin, from white willow (*Salix alba*) in 1827,[2,3] though salicin was poorly tolerated when taken internally due to gastrointestinal side effects.[2,3] Another important step in the history of aspirin was the first isolation of salicylic acid from *Filipendula ulmaira* flowers in 1839.[2] Salicylic acid is the compound to which salicin and related compounds are likely metabolized in the human body. Of note, the genus *Filipendula* was alternatively called *Spiraea*, part of the name given to the modern compound by the Bayer Corporation.[2] After the discovery of salicin and salicylic acid, the "modern" era of aspirin therapy was ushered in with the production of a related compound, acetylsalicylic acid in Germany in 1899,[2,3] which conveyed the analgesic, antipyretic, and anti-inflammatory effects of salicin and salicylic acid yet with a marked decrease in the adverse gastrointestinal effects.

Related Botanicals and Pharmacology

There are more than 300 species in the genus *Salix* (Family Salicaceae), many of which have a history of use for their anti-inflammatory effects.[4] One of the most well-known is white willow (*Salix alba*), and a treatment from ancient Greece used a decoction of *Salix alba* leaves placed on painful areas.[3] In addition to *Salix alba*, the bark of *S. purpurea* and *S. fragilis*, native to Europe and Asia, also are used. These two species are thought to have higher concentrations of the physiologically active phytochemicals than *S. alba*.[4]

Plants in the genus *Salix* have a variety of phenolic glycosides that account for the physiologic effects of these plants.[4] For example, the primary glycoside, salicin, and related glycosides, such as salicortin, fragilin, and tremulacin, all are converted to the active salicylic acid in the intestines and liver.[4] There is large species-by-species variability in the percentages of these glycosides, averaging about 7% by weight for *S. purpurea* and *S. fragilis*, but only about 1% for *S. alba*.[4] Many species of poplars (*Populus* spp.) also are known to have salicin in varying concentrations.[2]

As mentioned above, salicylic acid is found in *Filipendula ulmaria* (Family Rosaceae), as well as in wintergreen oil (*Gaultheria procumbens*, Family Ericaceae), and birch (*Betula lenta*, Family Betulaceae).

Despite the long tradition of use of ALB, it took until the 1970s for chemists to determine the pharmacologic activity of ASA. ASA binds to isoform 1 of cyclooxygenase (COX-1), and less so to the COX-2 isoform (hence, a nonselective COX-1/COX-2 inhibitor), causing irreversible enzyme inhibition and preventing arachadonic acid from accessing the active binding site, thereby limiting the production of the downstream prostaglandins that mediate pain and inflammation.[1] In addition, ASA has antiplatelet activity due to the inhibition of thromboxane A2 and decreased release of adenosine diphosphate; these effects can be achieved with low-dose daily ASA dosing.[1] It is thought that salicin, the primary ALB compound, has less than 50% of the activity of the salicylates like salicylic acid and ASA.[4]

Clinical Evidence: Aspirin and Related Botanicals

The primary focus of the medical literature has been on anti-inflammatory effects and cardiovascular protection from ASA and/or ALB. Overall, there are only sparse data for ALB. *Salix*, and mostly *Salix alba*, is the subject of a few clinical trials, all of which focus on its anti-inflammatory effects. There are no clinical trials for other ALB such as *Filipendula* spp, *Betula*, or *Gaultheria*, though there is some basic science research about *Gaultheria* phytochemicals.

Anti-inflammatory Effects

The traditional use of ASA for musculoskeletal complaints has been supported by numerous clinical trials

and meta-analyses.[5] Standard of care supports the use of NSAIDs, such as ASA, either as first-line or second-line therapy (after acetaminophen),[6] although this approach needs to be balanced with recent evidence for the possible increased cancer risk with the use of acetaminophen.[7] Predictably, perhaps, the ALB have less scientific evidence behind their clinical use as analgesics and anti-inflammatory treatments.

Salix alba is the most well-studied of the ALB for analgesia and anti-inflammatory activity, with clinical trails investigating its use for osteoarthritis, low back pain, headache (topical preparations), and rheumatoid arthritis. Three systematic reviews of herbal medicines found relevant articles for *Salix*. For example, between 1966 and July 2005, there were 10 studies examining herbal medicine for low back pain that met methodological criteria.[8] Three of the studies in this review investigated *S. alba*, finding short-term analgesic effects with 120-240 mg of salicin daily, approximately equivalent to 12.5 mg of rofecoxib. The results seemed to indicate more convincing effects with 240 mg of salicin daily. Another review looked at herbal preparations for osteoarthritis, and one of the five studies included described the evaluation of a combination herbal product with 100 mg of powdered *S. alba* bark plus four other plants in each tablet, and found pain relief in people with osteoarthritis.[9] With such a combination product, it is hard to tease out the specific contribution of willow to the clinical effects. Another review of botanical anti-inflammatory plants detailed one study of 21 patients with back osteoarthritis who had less pain when taking willow (240 mg of salicin daily) compared to a placebo group.[10]

One randomized trial was not part of the above reviews. The trial consisted of two parts: 127 people with osteoarthritis of the knee or hip randomized to 240 mg of salicin daily (from *S. daphnoides* bark), diclofenac 100 mg daily, or placebo, and 26 people with rheumatoid arthritis randomized to either 240 mg of salicin daily or placebo.[11] After six weeks, an intention-to-treat analysis revealed no reduction in pain for the salicin group when compared to placebo for either the osteoarthritis or rheumatoid arthritis groups. The diclofenac group had significantly more adverse effects (including gastrointestinal) than either the placebo or salicin groups, as well as decreases in hematocrit and hemoglobin, and elevations in liver function tests that were not present in the salicin groups. The authors hypothesized that these negative results could have been due to the *Salix* species used; each *Salix* species has a unique phytochemical spectrum beyond simply the salicin content, and some of the other compounds may contribute to clinical effects.

References were made above to salicylic acid being present in common wintergreen, *Gaultheria procumbens*, but related *Gaultheria* species also may have ALB effects. For example, a favorite plant of northwest Native Americans is salal (*Gaultheria shallon*), known to be high in antioxidants, though likely due mostly to the catechin and epicatechin polyphenols.[12] In addition, two basic science studies have been conducted on *Gaultheria yunnanensis*, a plant from China that has traditional use as an anti-inflammatory. This plant has high concentrations of salicylate-related phytochemicals, including gaultherin, similar in structure to salicylic acid.[13] It seems that gaultherin is metabolized to salicylate, leading to similar analgesic and anti-inflammatory effects as aspirin in animal models, but without the adverse gastric COX-1-mediated effects, though the authors were not entirely clear as to its exact mechanism of action.[13,14]

Cardiovascular Protection

As mentioned above, no clinical trials are listed in PubMed for ALB and stroke, myocardial infarction, or all-cause mortality prevention, as there are for ASA. The ASA literature is extensive, with numerous clinical trials, reviews, and meta-analyses on the topic.[1] For example, the Cochrane Collaboration has review articles on ASA and prevention of stroke or other serious cardiovascular events in high-risk adults,[15] the prevention of cardiovascular disease,[16] the treatment of acute ischemic stroke,[17] and the prevention of stroke in atrial fibrillation patients who had prior transient ischemic attacks or strokes,[18] among others. Aspirin, in the dose range of 50-325 mg daily, is considered adequate secondary preventive therapy for people with a history of stroke or transient ischemic attacks, with a stroke risk reduction of 15%-18% compared to placebo; the benefits of aspirin in this scenario may be augmented with extended-release dipyridamole.[19] Medical researchers also have explored the use of aspirin with and without clopidogrel for people with various cardiovascular risks; specific situations warrant certain combinations of these antiplatelet agents balancing the risk of hemorrhage with clinical benefits (see references 1 and 19 for a comprehensive discussion of the topic).

Dosage and Administration

Trying to connect the dosing of ALB to aspirin dosage recommendations is a challenge, primarily due to unknowns regarding the concentrations of salicin and related compounds in a given species and product. Some authors have attempted to calculate the amount of ALB needed to be ingested every day to meet current recommendations, and the volume of willow bark decoction is generally very high. For example, to obtain an anti-inflammatory effect similar to that of 4.5 g ASA, and assuming 50% clinical activity of salicin compared to the salicylates, more than five gallons of *Salix purpurea* bark tea would have to be ingested daily, a seemingly impossible amount.[4] Another

estimate was that the 240 mg of salicin studied in some clinical trials for pain relief was probably equivalent to approximately 50 mg of ASA.[20] The fact that such a low amount of ASA equivalents induced clinically significant pain relief has led some experts to postulate that the analgesic effect of *Salix* must be due to more than just the compound salicin. These dosages would be difficult to achieve even with raw herb in capsule form when 1 teaspoon is approximately 1.5 g of raw herb, and about 130 g of bark would have to be ingested daily to meet the dosages mentioned above.

Adverse Effects

The adverse effects of ALB would be expected to mimic those of ASA, including bleeding, allergic reactions in people with salicylate allergies, and hemolysis in people with glucose-6 phosphate deficiency.[21] ALB, as with ASA, should be avoided in any child suspected of having a viral infection due to concerns about the development of Reye's syndrome. With respect to antiplatelet effects, there is some indication that ASA blood thinning effects may not occur in the same way with ALB. For example, in one clinical trial, blood coagulation was said to be only "slightly affected" by 240 mg salicin daily from *S. alba*,[20] and in another trial, 240 mg of salicin (from *S. purpurea* and *S. daphnoides*) was compared to 100 mg of ASA and placebo in 68 people, finding that ASA was a better inhibitor of platelet aggregation than salicin ($P = 0.001$).[22] In fact, salicin's ability to inhibit platelet aggregation was similar to placebo in all but one of the parameters measured.

Conclusion

Aspirin-like botanicals predate acetylsalicylic acid, or aspirin, for use as analgesics and to fight inflammation. Most ALB have either salicin or its metabolite, salicylic acid, effective nonspecific COX inhibitors, though with an unacceptable gastrointestinal adverse effect profile in the purified forms. As powdered bark extracts, through some clinical trials of *Salix alba*, or white willow, there seems to be some anti-inflammatory effect in the setting of arthritis, with less antiplatelet effects and acceptable gastrointestinal tolerability. It is difficult to compete with the numerous clinical trials proving aspirin's cardioprotective effects, and its use as an anti-inflammatory. The fact that there is significant variability in salicin content and unpredictable, or unstudied, hematological effects with ALB speaks against the replacement of proven anticoagulants or antiplatelet therapy for primary or secondary prevention of cardiovascular events.

Recommendation

Aspirin needs to be the mainstay of our antiplatelet therapy for patients at risk of cardiovascular events. Its pairing with other antiplatelet agents may be necessary depending on the clinical scenario. Though at this point ALB don't appear to have a role in cardioprotection, they may be useful in the short-term, primarily as adjunctive therapy, for musculoskeletal pain in a dose of 240 mg salicin daily. ■

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Herbal Remedy Interactions with Warfarin and Aspirin

By Dónal P. O'Mathúna, PhD

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

A POPULAR IMPRESSION THAT HERBS ARE BASICALLY SAFE EXists along with a growing realization that some herbs interact with certain medications. Among potential interactions, one of significant concern is that between herbal remedies and anticoagulant medicines. The concern is highlighted in a survey of atrial fibrillation patients who were stabilized on warfarin.[1] Those who consumed herbs four or more times per week were more likely to have suboptimal anticoagulation control. Optimal control was defined as an international normalizing ratio (INR) of 2.0 to 3.0. Yet in a survey of English patients taking warfarin, almost 20% were taking herbal remedies concomitantly.[2] More than 90% had not discussed this with their health care professionals.

At least 180 dietary supplements have been noted as having the potential to interact with warfarin, and 120 with aspirin, clopidogrel, or dipyridamole.[3] However, such concerns usually are accompanied by an acknowledgment that little evidence is available on this topic beyond case reports. Yet case reports cannot substantiate claims of causation. Given that warfarin remains a very useful drug, and the frequency with which it is used along with herbal remedies, clinicians should be aware of the evidence available to advise patients taking anticoagulant drugs about their concomitant use of herbal remedies.

Pharmacology

Anticoagulant therapy generally involves warfarin, while aspirin and other pharmaceuticals are used for their antiplatelet effects. However, most of the reports on herbs and bleeding problems focus on warfarin. This may arise because clinicians pay more attention to warfarin than other medications, monitoring its dosing and relevant laboratory tests closely. Although warfarin has proved to be a very valuable medication, its pharmacology is complex and raises clinical challenges.[4] Individuals vary widely in their response to the medication, and regular monitoring is needed to ensure coagulation status remains stable. The average dose required is 5 mg/day, but individual needs range from 0.5 mg/day to 50 mg/day.[5] Warfarin has a narrow therapeutic index, where too little can result in thrombotic or embolic events, while too much can lead to bleeding or hemorrhage.[4]

Warfarin is metabolized by the cytochrome P450 system in the liver. The enzymes in this large and complex group are known individually as CYP enzymes. Factors that influence this enzyme system will impact warfarin's therapeutic effectiveness. Different herbs impact various CYP enzymes differently, making correlations between herbal remedies and warfarin even more challenging.[6] A growing number of herbs are known to impact this system, most notably St. John's wort.[6] Herbs, foods, and dietary supplements can affect warfarin in other ways. Some contain vitamin K, others interfere with warfarin absorption, and some have antiplatelet effects or can interfere with protein carriers used by warfarin.[6]

Clinical Studies

As mentioned above, dozens of different herbs have been linked with anticoagulant effects. A recent systematic review of all reported herb-drug interactions identi-

fied 128 published case reports, of which 108 were for St. John's wort.[6] Warfarin and aspirin were also associated with interactions with gingko, ginseng, and garlic. Therefore, this article will examine the evidence relating to these four commonly used herbal remedies.

Gingko

Several case studies have been published suggesting connections between gingko (*Gingko biloba*) and warfarin metabolism. Some of gingko's constituents have antiplatelet activity and are platelet-activating factor receptor antagonists.[6] These activities have been suspected of being linked to postoperative bleeding. Ginkgo contains several aglycones which have been shown to inhibit P450 enzymes in vitro.[4] However, for this to be clinically relevant, sufficient concentrations would need to accumulate in the liver to inhibit the enzymes in vivo. It is unclear whether this happens regularly.

Case reports have suggested that gingko leads to bleeding episodes in patients taking warfarin or aspirin.[6] However, a systematic review of such case reports failed to substantiate such concerns.[7] The review found that many case reports omitted crucial details which made it difficult to evaluate the role of gingko in the adverse events reported. With this, along with gingko's widespread usage, and the absence of bleeding problems in clinical trials that have involved almost 10,000 subjects, the reviewers concluded that the evidence does not support a causal link between gingko and bleeding.

A small number of controlled trials have been conducted in this area. In one, 50 healthy men were randomly assigned to receive either aspirin followed by aspirin plus ginkgo or vice versa.[8] Treatment lasted 7 days. No significant differences were found in bleeding times or platelet aggregation between the two treatment regimens. Another trial involved 55 older patients with peripheral artery disease who had been taking 325 mg aspirin daily.[9] They were randomly assigned to take 300 mg/day gingko or placebo for 4 weeks. No significant differences were found between the groups in a platelet function assay (PFA) or platelet aggregation.

In a controlled study, gingko failed to demonstrate an impact on warfarin anticoagulation in 24 patients on long-term warfarin therapy.[10] INR values did not change significantly between 4-week periods when patients were taking gingko, coenzyme Q10, or placebo. In another study, researchers gave a single dose of warfarin to 12 healthy men after 7 days pretreatment with ginkgo.[11] The men continued to take the herb for 7 days after the warfarin dose. INR values, platelet aggregation, and warfarin pharmacokinetics were not significantly different compared to when the men were given warfarin without any herb.

Another study involved 10 healthy adults whose PFA was measured with a PFA-100 analyzer.[12] Subjects were blinded to which one of five herbs they took for 2 weeks. Each herb was followed by a 2-week wash-out period and then another herb given for 2 weeks until all subjects had taken all five herbs. They also took 325 mg aspirin daily for 2 weeks. No significant changes were found in the PFA-100 results while taking gingko or any of the other herbs compared to baseline ($P > 0.10$). The results were significantly different after taking aspirin ($P < 0.02$). This study will be referred to below as the PFA-100 Study.

A systematic review of eight randomized controlled trials (RCTs) concluded that gingko does not cause significant changes in blood coagulation parameters in a clinically relevant manner.[13]

Ginseng

Extracts of Asian ginseng (*Panax ginseng*) have been shown to inhibit platelet aggregation in vitro.[6] However, case studies have reported both interfering and potentiating effects of ginseng on warfarin. Controlled trials have not confirmed that Asian ginseng affects platelet function. The PFA-100 study found that ginseng did not interfere with platelet function.[12] In another RCT, 25 patients newly diagnosed with ischemic stroke were assigned to either warfarin or warfarin with Asian ginseng.[14] After 2 weeks, INR and prothrombin time (PT) areas under the curve were significantly increased compared to baseline, but not significantly different between the groups. In another study, researchers gave a single dose of warfarin to 12 healthy men after 7 days pretreatment with ginseng.[15] The men continued to take the herb for 7 days after the warfarin dose. INR values, platelet aggregation, and warfarin pharmacokinetics were not significantly impacted by ginseng as compared to results obtained when warfarin was given when the men were taking no herbal remedies.

However, in one study, different results were found with American ginseng (*Panax quinquefolius*). Twenty healthy subjects were randomly assigned to either American ginseng or placebo for 2 weeks.[16] The impact of warfarin on INR was tested before and after the intervention phase. The peak INR, INR area under the curve, and peak plasma warfarin level all were significantly reduced in the ginseng group ($P = 0.0012$, 0.025, 0.026, respectively). The researchers speculated that these effects might be due to ginsenosides inducing liver enzymes.

Garlic

Case reports have suggested that garlic supplements might carry a risk of bleeding by influencing platelet function and coagulation.[6] Some indirect evidence based on ratios of drugs to their metabolites points to garlic having an impact on some CYP enzymes making up the P450 system. However, clinical trials have again failed to sub-

stantiate these interactions. A RCT enrolled 52 patients on warfarin therapy for a variety of vascular or cardiac conditions.[17] They were randomized to receive either aged garlic extract or placebo for 12 weeks. No significant differences were found in the number of bleeding-related adverse events between the groups.

The PFA-100 study discussed earlier included giving garlic to 10 people and did not find that it interfered with platelet function.[12] Another study gave a single dose of warfarin to 12 healthy men either alone or after 14 days pretreatment with garlic.[18] INR values, platelet aggregation, and warfarin pharmacokinetics were not significantly impacted by garlic.

St John's Wort

St John's wort (*Hypericum perforatum*) is an established inducer of P450 enzymes and thus can be expected to reduce the effectiveness of warfarin.[19] This effect appears to be related to hyperforin content, which is one of the constituents used to standardize some St. John's wort preparations. Extracts with low hyperforin content had a weak or no effect on P450 and other metabolic enzymes.[20] Accordingly, several case reports have been published where warfarin's anticoagulant effect was reduced in people taking St. John's wort concomitantly.[21] Such interactions have been confirmed in clinical trials that found reduced plasma concentrations of warfarin and phenprocoumon (an anticoagulant similar to warfarin) in those taking St. John's wort.[6,22]

In a clinical trial, a single dose of warfarin was given to 12 healthy men either alone or after 7 days pretreatment with St. John's wort.[15] The men continued to take the herb for 7 days after the warfarin dose. INR values and platelet aggregation were not significantly impacted by St. John's wort. However, the clearance rate of warfarin was significantly increased by St. John's wort, leading to a significantly reduced anticoagulant effect. The PFA-100 study did not find that St. John's wort interfered with platelet function.[12] This may reflect the lack of a direct effect on coagulation, while the other studies looked at St. John's wort's effect on warfarin's metabolism.

Conclusion

Given the widespread use of herbal remedies and anticoagulant therapy, little controlled research has been published on their interactions. Numerous case reports have been published suggesting correlations, but these reports suffer from many of the weaknesses of anecdotal reports. While gingko, Asian ginseng (*Panax ginseng*), and garlic have been associated with bleeding problems related to anticoagulant and/or antiplatelet therapy, the small number of clinical trials available have not substantiated these effects.

However, one controlled study has identified concerns with American ginseng (*Panax quinquefolius*). This found that American ginseng reduced warfarin's anticoagulant effect in young, healthy volunteers. Also, studies have confirmed that St. John's wort increases the metabolism of warfarin, thus reducing its anticoagulant effect.

Recommendations

Given the widespread use of herbal remedies, and warfarin's narrow therapeutic index, it is important that clinicians ask their patients about all herbal remedies they are taking. The results of controlled trials indicate that earlier concerns about gingko, Asian ginseng, and garlic interacting with anticoagulants may not be warranted. However, open and full discussion about herbal remedies between clinicians and patients should help to identify concerns or help when exploring adverse effects. At the same time, patients taking American ginseng or St. John's wort should be alerted to their interactions with warfarin.

The available research has important limitations that must be taken into account when discussing these issues with patients. In all areas, relatively few studies have been conducted involving small numbers of patients. Most were of short duration. In addition, each herb is available in numerous brands and used in varying doses. The results obtained in the studies reviewed here may or may not be applicable to the other available brands. Numerous other herbs and herbal mixtures — whose interactions with anticoagulant therapy have not been researched — are available. For such reasons, patients on anticoagulant therapies should be alerted to the potential for drug interactions and urged to have their bleeding times and/or INR/PT monitored carefully, especially when making changes to the herbs they consume. To facilitate collection of better data in this area, drug-herb interactions should be reported to the FDA MedWatch program (http://www.fda.gov/Safety/MedWatch). ■

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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

25. Of the herbal remedies reviewed here, the one with the best evidence to substantiate concerns about interactions with anticoagulant therapy is:

a. gingko.
b. Asian ginseng.
c. garlic.
d. St. John's wort.

26. The evidence that gingko may interfere with anticoagulant therapy comes from:

a. case studies alone.
b. case studies and analyses of constituents in gingko.
c. randomized controlled trials.
d. systematic reviews.

Answers: 25. d, 26. b.

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