

# Integrative Medicine

Evidence-based summaries and critical reviews on  
the latest developments in integrative therapies [ALERT]

## ANXIETY

### ABSTRACT & COMMENTARY

## Do Omega-3 Polyunsaturated Fatty Acids Play a Role in the Treatment of Anxiety?

By *Ellen Feldman, MD*

*Altru Health System, Grand Forks, ND*

Dr. Feldman reports no financial relationships relevant to this field of study.

**SYNOPSIS:** In a review and meta-analysis of 19 studies regarding use of omega-3 fatty acids for treating anxiety, researchers showed improvement in anxiety symptoms with these nutrients. The effect appears most significant in a clinically diagnosed subpopulation.

**SOURCE:** Su K, Tseng P, Lin P, et al. Association of use of omega-3 polyunsaturated fatty acids with changes in severity of anxiety symptoms: A systematic review and meta-analysis. *JAMA Netw Open* 2018;1:e182327.

*“Many lamentable effects this fear causeth in men, as to be red, pale, tremble, sweat; it makes sudden cold and heat come over all the body, palpitation of the heart, syncope, etc.”<sup>1</sup>*

— Robert Burton, 1621

**D**escribed almost 400 years ago by Robert Burton in *The Anatomy of Melancholy*, anxiety today holds the dubious distinction of ranking as the most common psychiatric condition. General anxiety disorder, panic disorder (with or without agoraphobia), separation anxiety disorder, social anxiety disorder, medication- or substance-induced anxiety, and specific phobias are among the disorders of anxiety described in the *Diagnostic and Statistical Manual of*

*Mental Disorders*. With prevalence of anxiety approaching one-third of the population, the healthcare costs and related indirect economic impact of anxiety disorders are significant. There are many options for intervention, but underrecognition and undertreatment often lead to worsening and prolongation of symptoms.<sup>2,3</sup>

It may be useful to consider how to distinguish anxiety from disorders of anxiety. As an emotional state, anxiety

**Financial Disclosure:** *Integrative Medicine Alert's* Executive Editor David Kiefer, MD; Peer Reviewer Suhani Bora, MD; Relias Media Executive Editor Leslie Coplin; Editor Jonathan Springston; and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

[INSIDE]

An Herbal Mixture  
for Enhanced Memory

page 28

Can Quality of Diet Lower the  
Risk of Depressive Symptoms?

page 30

Cinnamon for Dysmenorrhea:  
A Clinical Trial

page 34

*Integrative Medicine Alert* (ISSN 1096-942X) is published monthly by Relias LLC, 1010 Sync St., Ste 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Integrative Medicine Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

© 2019 Relias LLC. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Professional counsel should be sought for specific situations. This publication is not intended for use by the layman.

#### SUBSCRIBER INFORMATION

(800) 688-2421  
customerservice@reliamedia.com  
ReliasMedia.com

#### Questions & Comments:

Please contact Executive Editor Leslie Coplin, at [lcoplin@relias.com](mailto:lcoplin@relias.com)

#### Subscription Prices

United States  
Print: 1 year with free *AMA PRA Category 1 Credits™*, \$319  
Add \$19.99 for shipping & handling.  
Online only: 1 year (Single user) with free *AMA PRA Category 1 Credits™*, \$269

**Back issues:** \$42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and \$30 shipping.  
Elsewhere: Add \$30 shipping.

#### ACCREDITATION

Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCMME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

This CME activity is intended for physicians and researchers interested in integrative medicine. It is in effect for 36 months from the date of the publication.

## Summary Points

- Researchers conducted a systematic review and meta-analysis of 19 studies with 2,240 participants to determine the efficacy of omega-3 polyunsaturated fatty acids (PUFA) for treatment of anxiety symptoms.
- Hedges *g* (a measure of effect size) was significant (to  $P = 0.01$ ) for reducing clinical anxiety symptoms in the combined group of 1,203 participants receiving omega-3 PUFA.
- The anti-anxiety effect of omega-3 PUFA became significant only at doses of at least 2,000 mg per day. There was no significant anxiolytic effect detected at doses lower than this amount.

may occur as a healthy response to stress or unexpected events. However, anxiety disorders are diagnosed when the symptoms of anxiety are prolonged and begin to interfere with desired functions of life, such as sleeping, eating, working, and relationships.<sup>3</sup>

Conventional treatment of anxiety disorders includes psychological therapies (such as cognitive-behavioral therapy) alone or in combination with medication (typically, selective serotonin reuptake inhibitors, although other agents are possible).<sup>4</sup> Noting that anxious patients may avoid medication because of inherent heightened concern about side effects and that specific therapies may be difficult to access, Su et al stated that “evidence-based and safer treatments are required.”

Omega-3 polyunsaturated fatty acids (PUFAs) are fatty acids that are important in cell membrane structure as well as multiple other bodily functions. Most significantly, omega-3s help in the formation of signaling molecules that play essential roles in the cardiovascular, immune, endocrine, and pulmonary systems. The three main omega-3 PUFAs are alpha-linoleic acid (ALA) found in plant oils, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). EPA and DHA are found mainly in seafood and some algae. Notably, although ALA can be converted, albeit inefficiently, to EPA and DHA in the body, it is an essential fatty acid, which means that this nutrient is not synthesized naturally by the body. Thus, external sources of these agents — whether from foods or dietary supplements — are vital.<sup>5</sup>

Depression and anxiety often coexist. Omega-3 PUFAs have been found to have clinical utility in several studies of major

depressive disorder.<sup>6</sup> In a 2015 literature review of omega-3 PUFAs for depression, Wani et al found conflicting results in studies and pointed to the possibility that there exists a subtype of depression particularly susceptible to intervention with these agents.<sup>7</sup> Suominen-Taipale et al noted support from laboratory and some emerging clinical studies on the preventive potential of omega-3 PUFAs in both anxiety and mood disorders.<sup>8</sup>

Su et al stated that preclinical data from mouse and rat studies support the further exploration of omega-3 PUFAs for treating anxiety. They cited several animal studies with promising results, as well as a smattering of human case studies looking at this relationship. Noting that there had been no systematic review of the literature, Su et al sought to conduct a systematic review and meta-analysis of relevant clinical studies regarding anxiety and the use of omega-3 PUFAs.

Out of 3,584 studies and reports identified for potential inclusion in this review, only 19 studies were of sufficient quality to be included in this meta-analysis. Of the 19 studies, 16 included a placebo and all included a control group. A little more than half of the participants (1,203 participants out of a total respondent count of 2,240 participants) were treated with omega-3 PUFA.

Heterogeneity was a significant obstacle in this meta-analysis, with a wide range of scales used to measure anxiety. Another complicating factor was that the baseline condition of participants differed across the studies. Some studies included persons with a diagnosis of generalized anxiety but others included participants who had symptoms of anxiety caused by primary conditions

**Table 1: Subgroup Analysis**

- Subgroup 1: Patients receiving PUFA treatment vs. no PUFA treatment (19 studies)
  - Subgroup 2: Placebo-controlled trials (16 studies)
  - Subgroup 3: No clinical condition in participants, random selection from general population (5 studies)
  - Subgroup 4: Specific clinical diagnosis (14 studies)
  - Subgroup 5: Omega-3 PUFA dose < 2,000 mg/day (Specific types of omega-3 PUFA varied among the studies)
  - Subgroup 6: Omega-3 PUFA dose at least 2,000 mg/day (Specific types of omega-3 PUFA varied among the studies)
- PUFA: polyunsaturated fatty acids

(including attention deficit disorder, obsessive-compulsive disorder, post-myocardial infarction, post-trauma, Alzheimer’s disease, accidental injury, Parkinson’s disease, and test anxiety). Other studies included respondents recruited from the general population without any diagnosis. Su et al attempted to control for this heterogeneity, but clearly noted this as a limitation of the review.

Several subgroups were analyzed. Given the concerns about heterogeneity, Hedges g and 95% confidence intervals were employed to understand effect sizes. Hedges g is a measure of the difference between identified groups (effect size) and is similar to Cohen’s d. In this case, a Hedges g value of  $\geq 0$  indicates a higher association of anxiety reduction with omega-3 PUFA (vs. control). (See Tables 1 and 2.)

When combining results of all 19 studies (subgroup 1), there appeared to be a statistically significant association between taking omega-3 PUFAs and reduction of clinical

symptoms of anxiety. This association was even stronger when considering only the subgroup of participants with a specific diagnosis.

In addition, the investigators found some evidence that EPA-enriched supplements (> 50-60%) were beneficial in treating depression. However, in this meta-analysis, the more significant association with anxiolytic effect appeared to be with preparations with < 60% EPA.

#### ■ COMMENTARY

This ambitious, well-designed meta-analysis consolidated 19 disparate studies linked together by an interest in investigating the effect of omega-3 PUFAs for treatment of anxiety. The results showed an association toward effective anxiolytic action with use of these agents, especially in cases in which there was a defined clinical diagnosis (neuropsychiatric or medical).

As noted previously and discussed by Su et al, the major limitation of this review resides within the heterogeneity of the 19 studies. There is clear evidence that the study authors not only were looking at very different aspects and manifestations of anxiety, but also were using different scales to measure anxiety and response to intervention. Breaking the total group into specific subgroups helps address this deficit, but leads to much smaller numbers in each group, making it difficult to generalize these results.

This dilemma points to the need for more well-designed and robust studies with clear criteria for diagnosis and standardized scales for measurement. For example, anxiety symptoms associated with traumatic events may require a different intervention than anxiety associated

**Table 2: Trial Results**

n = Number of Studies	Characteristics of Subgroup	Hedges g	Confidence Interval	P Value
<b>Subgroup 1 (n = 19)</b>	<b>PUFA vs. no PUFA</b>	<b>Hedges g = 0.374</b>	<b>0.081-0.666</b>	<b>0.01</b>
<b>Subgroup 2 (n = 16)</b>	<b>Placebo-controlled</b>	<b>Hedges g = 0.372</b>	<b>0.032-0.712</b>	<b>0.03</b>
Subgroup 3 (n = 5)	No clinical condition (healthy volunteers)	Hedges g = - 0.008	-0.266 to 0.250	0.95
<b>Subgroup 4 (n = 14)</b>	<b>Clinical diagnosis (ADHD, obsessive-compulsive disorder, Tourette’s syndrome, severe injury, Parkinson’s disease, trauma, premenstrual syndrome, Alzheimer’s disease, test anxiety, depression)</b>	<b>Hedges g = 0.512</b>	<b>0.119-0.906</b>	<b>0.01</b>
Subgroup 5 (n = 9)	Omega-3 PUFA < 2,000 mg/day	Hedges g = 0.457	-0.077 to 0.991	0.09
<b>Subgroup 6 (n = 11)</b>	<b>Omega-3 PUFA at least 2,000 mg/day</b>	<b>Hedges g = 0.213</b>	<b>0.031-0.395</b>	<b>0.02</b>

Bold = statistically significant; PUFA: polyunsaturated fatty acids

with a neurodegenerative disorder such as Parkinson's disease or Alzheimer's disease, and these both may differ substantially from interventions needed to address test anxiety. The material and data available now is useful for only preliminary conclusions, but does point to a direction for future work in this area.

When weighing risk and harm, it is noteworthy that there is little harm associated with use of omega-3 PUFAs, especially with doses in the range of 2,000 mg/day.<sup>4</sup> On the other hand, the effect of untreated anxiety on clinical conditions is significant and can lead to prolongation or worsening of medical states in conditions as disparate as multiple sclerosis, cardiovascular disease, and pulmonary disease.<sup>9,10</sup> In mental illness, untreated anxiety is a risk factor for complications of multiple disorders and is an independent risk factor for suicide.<sup>11</sup>

Given these considerations, a primary care or integrative provider can solidly recommend that patients with anxiety consider a role for dietary intervention with omega-3 PUFAs. The potential for omega-3 PUFAs in fighting anxiety symptoms may be of particular interest to patients who are hoping to avoid conventional pharmacologic agents, including many women of childbearing age and patients who have multiple comorbidities and are hoping to avoid or minimize polypharmacy.

It is useful to keep in mind that there is no evidence from the studies in this review that omega-3 PUFAs can replace traditional antianxiety agents or therapies, and no evidence to support or discourage a combination of these agents. The take away? There is good evidence to support further investigation into the use of omega-3 PUFAs for the treatment of anxiety. The doses of these

agents look to be most efficacious at  $\geq 2,000$  mg/day. The effect is most pronounced in people with anxiety associated with a clinically diagnosed disorder. There is clear and exciting potential for not only clinical guidelines but also public health interventions to emerge as more robust and rigorous studies examine the role of omega-3 PUFAs treatment of anxiety disorders. ■

#### REFERENCES

1. Burton R. *The Anatomy of Melancholy*. London, UK: 1621.
2. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci* 2015;17:327-335.
3. Kupfer DJ. Anxiety and DSM-5. *Dialogues Clin Neurosci* 2015;17:245-246.
4. Bystritsky A, Khalsa SS, Cameron ME, Schiffman J. Current diagnosis and treatment of anxiety disorders. *PT* 2013;38:30-57.
5. National Institutes of Health. Office of Dietary Supplements. Omega-3 Fatty Acids. Available at: <https://ods.od.nih.gov/factsheets/Omega-3FattyAcids-HealthProfessional/>. Accessed Dec. 29, 2018.
6. Appleton KM, Perry R, Sallis HM, et al. Omega-3 fatty acids for depression in adults (Protocol). Available at: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004692.pub3/epdf/full>. Accessed Jan. 15, 2019.
7. Wani AL, Bhat SA, Ara A. Omega-3 fatty acids and the treatment of depression: A review of scientific evidence. *Integr Med Res* 2015;4:132-141.
8. Suominen-Taipale AL, Partonen T, Turunen AW, et al. Fish consumption and omega-3 polyunsaturated fatty acids in relation to depressive episodes: A cross-sectional analysis. *PLoS One* 2010;5:e10530.
9. Morrow SA. Anxiety is more important than depression in MS – Yes. *Mult Scler* 2018;24:440-441.
10. Xiao T, Qiu H, Chen Y, et al. Prevalence of anxiety and depression symptoms and their associated factors in mild COPD patients from community settings, Shanghai, China: A cross-sectional study. Available at: <https://bmcpyschiatry.biomedcentral.com/articles/10.1186/s12888-018-1671-5>. Accessed Dec. 29, 2018.
11. Nepon J, Belik SL, Bolton J, Sareen J. The relationship between anxiety disorders and suicide attempts: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Depress Anxiety* 2010;27:791-798.

## MEMORY

### ABSTRACT & COMMENTARY

# An Herbal Mixture for Enhanced Memory

By David Kiefer, MD, Editor

**SYNOPSIS:** These researchers showed that a tincture of sage, rosemary, and lemon balm improved one aspect of cognition after two weeks in healthy people.

**SOURCE:** Perry NSL, Menzies R, Hodgson F, et al. A randomised double-blind placebo-controlled pilot trial of a combined extract of sage, rosemary and melissa, traditional herbal medicines, on the enhancement of memory in normal healthy subjects, including influence of age. *Phytomedicine* 2018;39:42-48.

There is a growing body of evidence that spices may play an important physiologic role. Some past reviews in *Integrative Medicine Alert* have addressed some of the recent findings. In addition, there is the interest in the ethnobotanical research community to investigate the biochemical basis for and the clinical effects of “traditional remedies,” or those treatments that, throughout history, have been used in cultures around the world.

This clinical trial by Perry et al brings together these two lines of inquiry: exploring the effect of an herbal spice combination on memory in healthy research participants.

The authors began their article with a compelling review of the physiological effects of some plants on processes relevant to neurological function. They mentioned sage

## Summary Points

- An ethanolic extract (tincture) of sage, rosemary, and lemon balm was administered to 22 people twice daily for two weeks and compared to 22 people in a placebo group.
- For a subgroup of subjects younger than 63 years of age, the herbal mixture enhanced delayed word recall compared to baseline and compared to the placebo group.

(*Salvia officinalis*, the common culinary sage species), bacopa (*Bacopa monnieri*, a plant with roots in Ayurvedic medicine), turmeric (*Curcuma longa*), peppermint (*Mentha x piperita*), ginkgo (*Ginkgo biloba*), saffron (*Crocus sativus*), lemon balm (*Melissa officinalis*), and rosemary (*Rosmarinus officinalis*). They also cited studies showing positive effects on oxidation and inflammation, as well as effects that might classify the plants as “neuroprotectants.” From this information, the researchers honed their list to sage, rosemary, and lemon balm (which they called melissa) because there are studies supporting their “traditional use for cognitive function.” After assuring themselves of the three plant identities, they placed 0.5 grams of the plants per milliliter of 45% ethanol for three weeks in a dark room (a typical process for making a tincture). At the end of the extraction period, the liquid was placed in 50 mL bottles. The placebo extract was made with sweet cicely (*Myrrhis odorata*) by using 1 g/mL with 45% ethanol. Sweet cicely is a plant not known to affect cognitive function. Of note, sweet cicely was added to the treatment extract to account for 10% of the volume. With respect to study protocol dosing, the treatment extract was administered to those participants in the treatment group at a dose of 5 mL in warm water twice daily for two weeks. The placebo group received 5 mL of the placebo liquid twice daily for two weeks.

The study took place in the United Kingdom. To be included in the study, participants needed to be at least 40 years of age and “healthy,” with no reports of mental impairment or related diagnosis. People could not participate if they were taking warfarin, were pregnant or breastfeeding, or presumably had any condition or diagnosis that might label them as “unhealthy.”

At baseline (day 0) and at the end of the study period (day 14), study participants underwent a memory test. For this, the participants were tested on their abilities to recall 15 words both immediately and delayed. These words were displayed on cards individually to the participants and then they were asked to write down as many as they could remember in one minute. Ten minutes later, once again they were asked to write down

**Table 1: Trial Results**

Mean number of words recalled at baseline (day 0) and post-study (day 14) results for the treatment group and the placebo group. Both immediate word recall and delayed word recall are included in the table.

		<b>Baseline (immediate/ delayed)</b>	<b>Post-study (immediate/ delayed)</b>
Younger (≤ 62 years of age)	Placebo	7.4/5.6	7.3/5.4
	Treatment	6.9/4.6	<b>7.2/7.2</b>
Older (≥ 63 years of age)	Placebo	6.2/5.0	6.2/4.5
	Treatment	6.0/4.2	6.0/3.5

as many of the 15 words that they could remember. The results of these tests were recorded simply as the number of words recalled.

Forty-four of 45 recruited subjects completed the study protocol. Baseline word recall was statistically similar between the treatment and placebo groups. (See Table 1.) The researchers split these analyses into older vs. younger age groups, which in fact may have occurred *after* they noticed that the placebo group had a mean age 4.5 years younger than the treatment group. All told, there were minimal differences in word recall counts for any time points and age/treatment status. They only called out one result: the 7.2 words of delayed recall for the younger treatment group at day 14. (See *bold value*, Table 1.) This was mentioned as statistically different from the corresponding placebo value of 5.4 ( $P = 0.0347$ ) and much improved over the baseline value of 4.6 ( $P = 0.0123$ ).

No adverse effects were documented in any of the study subjects. In addition, there were no conflicts of interest nor concerns about funding that would taint the results presented here.

### ■ COMMENTARY

As introduced in the first part of this review, this research study weaved an exploration of traditional remedies with the idea that spices and other herbal medicines might have tangible medicinal benefits. In addition, by studying a healthy population, the results nudge the reader to imagine how plants might promote wellness and serve as effective preventive treatments. Yes, these are high expectations, but the findings do seem to meet some of these parameters.

In some respects, the study might best be considered as a pilot study. On the positive side, the authors provided a lot of details about the plant preparation, including information about plant identification and the creation of the tinctures; it is useful and important to understand plant dosing and specifics relevant to clinical use. The

authors described the placebo development and that it is a randomized, controlled trial. To be complete, they should have expanded on the one participant dropout and explained the randomization and blinding processes. On that note, technically, to be the most statistically accurate, the researchers would have used an intention-to-treat analysis, accounting for the one study dropout and detailed why the person dropped out, as well as from which group he or she dropped out, which was not done. However, given the low dropout number, this may not have made much of a statistical difference. Furthermore, it is unclear how standard word recall testing is for assessing subtle cognitive changes in a healthy population.

The researchers could have provided more justification for their methodology here. Perhaps a fatal statistical flaw was the adjustment of the analysis *after* noticing that there was potentially an age effect. A more ideal recruitment and randomization process would have included age in the process at the beginning of the trial. The authors had lofty goals, namely to find and promote

“effective treatments and preventive strategies” addressing concerning trends for the incidence and prevalence of Alzheimer’s disease worldwide. Since this was a study in a healthy population, we are unable to apply the findings to those with a dementia diagnosis and feel confident that we will find the same effects. In addition, the benefits seen here were in a younger cohort, not the age at which Alzheimer’s disease is more commonly diagnosed. Just as it is difficult to conclude that clinicians should adjust their clinical practice for dementia treatment based on these results, it is also difficult to comment on herbal form and dosing other than exactly what was used in this trial. Rosemary and sage, common culinary spices, are used most often in doses lower than what was used in this study, so a food use of these two plants may not necessarily bring about “brain-enhancing” benefits. In addition, an alcohol extraction could yield different chemical and physiological properties than a water extraction (infusion or tea) or in a food recipe. These results are an intriguing first step in the search for tools to prevent, and maybe treat, cognitive decline or dementia. ■

## DEPRESSION

### ABSTRACT & COMMENTARY

# Can Quality of Diet Lower the Risk of Depressive Symptoms?

By *Ellen Feldman, MD*

*Altru Health System, Grand Forks, ND*

Dr. Feldman reports no financial relationships relevant to this field of study.

**SYNOPSIS:** In a meta-analysis of 42 studies, researchers found that subjects who reported following the Mediterranean diet closely had a 0.67 reduced risk of developing depressive symptoms compared with low adherence to this diet.

**SOURCE:** Lassale C, Batty GD, Baghdadli A, et al. Healthy dietary indices and risk of depressive outcomes: A systematic review and meta-analysis of observational studies. *Mol Psychiatry* 2018; Nov 21. doi: 10.1038/s41380-018-0299-7. [Epub ahead of print].

Lassale et al noted mixed results from the literature regarding diet and depressive symptoms. Citing several factors, such as variable methodology both when defining diet and measuring depressive symptoms that could be contributing to these mixed results, they conducted this meta-analysis to pool and analyze results from studies using specified dietary indices and a standardized approach to measuring depressive symptoms.

More than 300 million people worldwide live with depression. The prevalence varies worldwide and generally is higher in more developed countries. Debilitation from untreated or unresponsive depressive disorders contribute to an estimated productivity loss to the global economy of \$1 trillion per year.<sup>1,2</sup> In 2016, an estimated 16.2 million U.S. adults had at least one depressive episode, and the prevalence among adult women and men was

8.5% and 4.8%, respectively. Children also are affected, but at a lower rate. Sadness, apathy, somatic symptoms, poor concentration, and sleep disturbance are among the symptoms of this often chronic psychiatric disorder.<sup>3</sup>

To be included in this comprehensive review and meta-analysis, depression had to be documented by a clinician or study staff or measured by a validated scale or questionnaire. Even within these parameters, the measurement of depression varied among the 42 studies, with methods ranging from self-reported physician diagnosis to antidepressant use to 10 different scales, including Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS), and Moods and Feelings Questionnaire (MFQ). All longitudinal studies excluded subjects with depressive symptoms or depressive disorder at the start of the study.

## Summary Points

- The authors of this meta-analysis incorporated 42 observational studies (20 longitudinal) investigating the degree of compliance to a predefined healthy diet and the emergence of depressive symptoms or depressive disorder.
- Most dietary guidelines used in the study followed the Mediterranean diet, the Healthy Eating Index, the Alternative Healthy Index, the Dietary Approach to Stop Hypertension, and the Dietary Inflammatory Index.
- The most robust evidence was found in subjects with high adherence to the Mediterranean diet. They had a 33% reduced risk of depression when compared with low adherence to the diet.
- Comparing the least inflammatory to the most inflammatory diet revealed a 24% reduction in depressive outcomes among participants in five longitudinal studies. A limiting factor was significant heterogeneity among these studies.

Dietary indices reflect compliance with specified dietary patterns; thus, a dietary index gives a composite measure of diet quality. Lassale et al found few studies comparing dietary indices between various healthy diets so they conducted a separate meta-analysis for each dietary pattern. In each meta-analysis, the group compared depressive symptoms in highest to lowest adherence to the diet. Longitudinal studies were given extra weight over cross-sectional studies because of the concern that the relationship between diet and depressive symptoms is not a one-way street — mood may influence diet just as easily as diet can affect mood. Every study used food frequency questionnaires to monitor and record dietary compliance and adherence. Most of the studies included information about diet at one point in time rather than on a continuum, although the frequency differed depending on study length. Below are brief descriptions of each diet and/or dietary index and results of meta-analysis.

### **Mediterranean Diet: four dietary indices; six longitudinal and three cross-sectional studies**

In general, this well-known diet emphasizes green leafy vegetables, fruits, whole grains, fish, nuts, and beans, with olive oil as the principal source of fat.<sup>4</sup> Across the studies, four different indices were used to measure adherence to this diet: the original Mediterranean Diet score (MDS), the relative Mediterranean Diet Score (rMDS), the alternative Mediterranean Diet Score (aMDS), and the Mediterranean Style Dietary Pattern Score (MSDPS). Each index includes slightly different foods and different

cutoff scores to measure degree of adherence to the specified diet.

Results from four longitudinal studies (36,556 respondents) were analyzed to estimate the relative risk of developing depressive symptoms when comparing high to low adherence to this diet. A relative risk of 0.67 (95% confidence interval [CI], 0.55-0.82) was calculated for this group. (See Table 1.) Two additional longitudinal studies were not included because of incompatible methodology. Results of the three cross-sectional studies were not consistent.

### **Healthy Eating Index (HEI); three dietary indices; three longitudinal and four cross-sectional studies**

The HEI measures diet quality in accordance with recommendations of the Dietary Guidelines for Americans. These guidelines shape federal nutrition standards and policies for relevant national programs. The three indices used were the original AHEI, the AHEI-2005, or the AHEI-2010. Each includes slightly different components and score ranges.<sup>5</sup>

Results from three longitudinal studies (45,533 respondents) were analyzed to estimate the relative risk of developing depressive symptoms when comparing high to low adherence to this diet. A relative risk of 0.76 (95% CI, 0.57-1.02) was calculated for this group, but concerns about significant heterogeneity limit the usefulness of these results. (See Table 2.)

### **Dietary Inflammatory Index (DII); one index; five longitudinal and four cross-sectional studies**

The DII is based on an algorithm calculating the inflammatory potential of foods. The raw score often is converted into a “grade” reflecting level of inflammation. The DII is based on the understanding that inflammation plays a role in many chronic conditions and that inflammation on a vascular level can be modified by diet. Extensive literature searches calculating the inflammatory potential (and anti-inflammatory potential) of numerous food items led to the development of this index. Forty-five food “parameters,” including macronutrients and micronutrients, as well as some whole foods such as ginger and garlic, are scored according to inflammatory potential, with a range of -10 to 10. Higher scores reflect greater inflammatory potential.<sup>6,7</sup>

Results from five longitudinal studies (31,416 respondents) were analyzed to estimate the relative risk of developing depressive symptoms when comparing the least inflammatory to the most inflammatory diets. A relative risk of 0.76 (95% CI, 0.63-0.92) was calculated for this group. However, Lassale et al noted significant heterogeneity possibly because of gender differences. Three of these studies found no relationship between DII and depressive symptoms in men, while one study found the association only in men and not in women. (See Table 3.)

**Table 1: Characteristics of 4 Longitudinal Studies Examining the Mediterranean Diet and Depressive Outcomes**

Study Author; Year	Dietary Index	Number of Participants	Length of Study (Years)	Country
Adjibade; 2017	rMED	2,013 men; 1,492 women	12.6 years	France
Hodge; 2013	MDS with olive oil	8,660	11 years	Australia
Sanchez Villegas; 2015	MDS	15,093	8.5 years	Spain
Lai; 2016	DQES	9,280	12 years	Australia

MDS: Mediterranean diet score, rMDS: relative Mediterranean diet score, MSDPS Mediterranean style dietary pattern score, DQES: Dietary Questionnaire for Epidemiological Studies

**Table 2: Characteristics of 3 Longitudinal Studies Examining the Healthy Eating Index and Depressive Outcomes**

Study Author; Year	Dietary Index	Number of Participants	Length of Study (Years)	Country
Adjibade; 2018	AHEI-2010	26,225	5.9 years	France
Akbaraly; 2013	AHEI	4,215	5 years	United Kingdom
Sanchez Villegas; 2015	AHEI-2010	15,093	8.5 years	Spain

AHEI: American Healthy Eating Index

**Table 3: Characteristics of 5 Longitudinal Studies Examining the Dietary Inflammatory Index and Depressive Outcomes**

Study Author; Year	Dietary Index	Number of Participants	Length of Study (Years)	Country
Akbaraly; 2016	DII	4,246	5 years	United Kingdom
Adjibade; 2017	DII	2,031	12.6 years	France
Sanchez Villegas; 2015	DII	15,093	8.5 years	Spain
Shivappa; 2016	DII	6,438	9 years	Australia
Shivappa; 2016	DII	3,608	8 years	United States

DII: Dietary Inflammatory Index

### Dietary Approaches to Stop Hypertension (DASH); one index; one longitudinal study and three cross-sectional studies

The DASH plan, developed to combat hypertension or prehypertension with or without pharmacologic intervention, is rich in vegetables, fruits, low-fat dairy, and whole grains. In general, high-sodium foods, fatty foods, and foods or beverages with high sugar content are avoided.<sup>8</sup> The DASH diet score or a modified version of the same was used in all studies. In the only longitudinal study, the Fung DASH diet score was compared to modified versions. There was an inverse association with depression only when using the Fung DASH dietary index. Given these results and the limited number of studies, no conclusions were drawn about an association with depressive symptom reduction.

### ■ COMMENTARY

Depression can be relatively easy to recognize but more difficult to treat. The *Diagnostic and Statistical Manual*

*of Mental Disorders* defines eight subtypes of depression, including major depressive disorder, depressive disorder due to another medical condition, premenstrual dysphoric disorder, and unspecified depressive disorder. There are clear and specific diagnostic criteria for each. Central to all depressive disorders is a functional impairment due to change in mood.<sup>9</sup> However, each subtype presents under different circumstances and may require nuanced intervention. In the pooled results covered by the meta-analysis, the subtypes were not specified nor was there a consistent distinction between clinical depression and depressive symptoms. These two factors alone may contribute to the heterogeneity and may have skewed the results. Clarification in future studies should assist in developing more compelling, generalizable conclusions.

The first-line treatment for most forms of depressive disorders is conventional medication combined with specific psychotherapies. However, compliance with these interventions tends to be limited and variable.

Psychotherapy can be difficult to access. Financial barriers, geographical barriers, the time commitment, and stigma may discourage some from seeking this potentially powerful intervention.

Antidepressants are not always well accepted either. Authors of a study of 367 people with depression found that more than 50% of the group discontinued antidepressants within the first six months of treatment. Additionally, more than 60% of those who stopped taking antidepressants did so without consulting a physician.<sup>10</sup> Even under optimal conditions, investigators have noted that conventional treatment is effective in only one in three cases of depressive disorder, making prevention a priority for intervention.<sup>11</sup>

Clinicians working with depressed patients often become aware that a barrier to implementation of any intervention is the lower energy, more negativity, and decreased motivation that accompanies this disorder. The authors of the studies in this meta-analysis pointed to diet as a potential preventive agent for treating depression. Reducing or preventing symptoms before full-blown clinical depression emerges is a major goal in the treatment of depression and could alter the course of the disorder in a positive direction.<sup>11</sup>

Notably, Lassale et al did not address dietary intervention in patients with clinical depression at the onset of the study. Although certainly there is suggestive evidence of a link, rigorous studies with standardized diagnostic criteria are needed before clinicians can draw conclusions regarding this population.

In a January 2019 guest editorial published in the *Psychiatric Annals*, Dr. Louisa Sylvia noted that despite the promise of integrative modalities in treating depression, interventions such as “exercise, yoga, nutrition, and mindfulness” tend to be neglected, with at most 30% of providers prescribing any one of these for a patient. Her thought is that clinician acceptance and use of these modalities may increase with clear evidence of efficacy.<sup>12</sup>

This meta-analysis regarding dietary index and the risk of depressive outcomes is a step forward toward synthesizing evidence for the efficacy of nutritional intervention in depression. Although the limitations cannot be overlooked, Lassale et al showed clear observational evidence of a link toward reduced risk of depressive symptoms or clinical depression with adherence to a Mediterranean diet and/or avoidance of a pro-inflammatory diet.

Perhaps the limitations of the reviewed studies are as important as the positive findings. That is, emerging from this review is a mandate for future studies in this field to be prospective and long-term to control for reverse causality. Additionally, establishing a gold-standard measurement to determine severity of depressive

symptoms, distinguish between depressive symptoms and full-blown clinical diagnosis, and move away from food frequency questionnaires toward a more precise instrument to quantify diet over time will help these studies gain legitimacy and validity. The proposed mechanism of dietary intervention for depression revolves around the theory that diet can lead to oxidative stress and inflammation, both of which cause neuronal damage. Foods with antioxidant and anti-inflammatory characteristics, such as fruit, vegetables, and nuts, can reduce or reverse this damage. Recent work points to the microbiota-gut-brain axis, an intimate connection between gut microbials and the brain. It is thought that modification of gut microbiota via diet can alter neurotransmission and influence neuropsychiatric disorders such as depression.<sup>13</sup>

While research in the field continues, there is no need to delay implementing results of this meta-analysis into clinical practice. There are no drawbacks or downsides to recommending healthy dietary interventions such as the Mediterranean diet and/or avoiding pro-inflammatory foods when discussing depression or prevention of this disorder. On the other hand, the clear potential benefits in reducing the burden of depression or avoiding this disorder altogether by incorporating diet change into treatment is compelling. Patients experiencing severe depression may find it difficult to muster the energy needed to plan and modify a diet. Catching such patients (those at risk for depressive episodes) at early stages may help lower this barrier. Providers should discuss diet with patients and help them adopt such an intervention into an overall treatment and wellness plan. ■

## REFERENCES

1. World Health Organization. Depression. Available at: <https://www.who.int/news-room/fact-sheets/detail/depression>. Accessed Jan. 22, 2019.
2. World Health Organization. Depression and Other Common Mental Disorders. Global Health Estimates. Available at: <https://bit.ly/2S57PDq>. Accessed Jan. 22, 2019.
3. National Institute of Mental Health. Major Depression. Available at: <https://www.nimh.nih.gov/health/statistics/major-depression.shtml>. Accessed Jan. 20, 2019.
4. UCSF Weill Institute for Neurosciences. Memory and Aging Center: The Mediterranean Diet Pyramid. Available at: <https://memory.ucsf.edu/sites/memory.ucsf.edu/files/MediterraneanDietHandout.pdf>. Accessed Jan. 20, 2019.
5. United States Department of Agriculture. Healthy Eating Index. Available at: <https://www.cnpp.usda.gov/healthyeatingindex>. Accessed Jan. 16, 2019.
6. Cavicchia PP, Steck SE, Hurley TG, et al. A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. *J Nutr* 2009; 139:2365-2372.
7. Shivappa N, Steck SE, Hurley TG, et al. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* 2013; 17:1689-1696.
8. National Heart, Lung, and Blood Institute. In Brief: Your guide to lowering your blood pressure with DASH. Available at: [https://www.nhlbi.nih.gov/files/docs/public/heart/dash\\_brief.pdf](https://www.nhlbi.nih.gov/files/docs/public/heart/dash_brief.pdf). Accessed Jan. 26, 2019.
9. Psychiatry Online. DSM Library. Available at: <https://dsm.psychiatryonline.org/doi/10.1176/appi.books.9780890425596.dsm04>. Accessed Jan. 20, 2019.

10. Sawada N, Uchida H, Suzuki T, et al. Persistence and compliance to antidepressant treatment in patients with depression: A chart review. Available at: <https://bmcp psychiatry.biomedcentral.com/track/pdf/10.1186/1471-244X-9-38>. Accessed Jan. 22, 2019.
11. van Zoonen K, Buntrock C, Ebert DD, et al. Preventing the onset of major depressive disorder: A meta-analytic review of psychological interventions. *Int J Epidemiol* 2014;43:318-329.
12. Healy. *Psychiatric Annals*. Finding solutions for treating depression. Available at: <https://bit.ly/2HuCaAf>. Accessed Jan. 24, 2019.
13. Sandhu KV, Sherwin E, Schellekens H, et al. Feeding the microbiota-gut-brain axis: Diet, microbiome, and neuropsychiatry. Available at: <https://www.sciencedirect.com/science/article/pii/S193152441630264X>. Accessed Jan. 22, 2019.

## WOMEN'S HEALTH

### ABSTRACT & COMMENTARY

# Cinnamon for Dysmenorrhea: A Clinical Trial

By David Kiefer, MD, Editor

**SYNOPSIS:** Cinnamon, three grams daily, for the first few days of menstruation may help attenuate menstrual pain in women suffering from dysmenorrhea, although an improved follow-up clinical trial is necessary to corroborate this.

**SOURCE:** Jahangirifard M, Taebi M, Dolatian M. The effect of cinnamon on primary dysmenorrhea: A randomized, double-blind clinical trial. *Complement Ther Clin Pract* 2018;33:56-60.

**P**remenstrual disorders, which encompass a variety of affective and somatic symptoms, are common, with some estimates that 12% of women meet the criteria for premenstrual syndrome (PMS).<sup>1</sup> Several classes of medications are available to treat PMS, but some women also turn to integrative therapeutics for symptomatic relief.<sup>1</sup> To explore one treatment that falls under the latter category, Jahangirifard et al focused on the effects of cinnamon. Cinnamon, an omnipresent spice, is a common name that refers to several species of plant that yield products with culinary and medicinal use. It is likely that these authors used true, or Ceylon, cinnamon (*Cinnamomum verum*, Family Lauraceae), considered more “delicate” and “complex” in flavor.<sup>2</sup> Another commonly sold cinnamon species, and one that also can be called “cinnamon” legally in the United States, is cassia cinnamon (*Cinnamomum aromaticum*, synonym *Cinnamomum cassia*). It is sweeter and stronger in flavor than true cinnamon and often is less expensive.<sup>3</sup>

Jahangirifard et al focused on documented and cited anti-inflammatory effects of cinnamon as justification for undertaking this PMS study. This study was conducted at Isfahan University of Medical Sciences in Iran, and the researchers recruited 80 female students from the university. Inclusion and exclusion criteria are listed in Table 1, but research participants had to complete a “verbal multidimensional scoring system” (VMS) rating during the recruitment process showing “mild” or “moderate” menstrual pain. No scale was provided to determine these VMS categories.

Eighty women were randomized to receive either capsules of cinnamon (n = 40) or placebo (n = 40). Each cinnamon capsule contained 1,000 mg cinnamon, while the placebo capsules contained 1,000 mg starch (presumably corn starch, but this was not specified).

### Summary Points

- This was a double-blind, placebo controlled trial that included 80 women with mild-moderate menstrual pain.
- Research subjects were given 1,000 mg of the cinnamon spice (presumed true cinnamon) or 1,000 mg of matching starch capsule three times daily for the first three days of menstruation for two cycles.
- Both groups improved over time, but there was a more pronounced pain-relieving effect in those taking cinnamon.
- Several significant methodological flaws in this paper compromised the believability of the results.

Patients took each capsule three times daily for three days, starting on the first day of the menstrual period. The three-day treatment was administered for two menstrual cycles. Women were asked to rate their menstrual pain using a visual analog scale (VAS) from 0 (no pain) to 10 (severe pain) at baseline and after each of the three-day treatments.

After the allocation to treatment or placebo, no women were lost to follow-up, although 12 in the cinnamon group and 10 in the placebo group stopped the protocol for one of four reasons: “irregular consumption,” taking pain medications, allergic reaction, or “missing drugs.” The researchers only analyzed data from those who completed the protocol (28 in the cinnamon group and 30 in the placebo group).

**Table 1: Criteria for Inclusion or Exclusion From the Research Study**

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>Mild to moderate menstrual pain during menstruation</li> <li>Regular (21-38 days) menstrual cycle</li> <li>Negative gynecological history</li> <li>No systemic diseases</li> <li>No allergies to herbal medicines</li> </ul>	<ul style="list-style-type: none"> <li>Severe menstrual pain during menstruation</li> <li>Menstruation less than 21 days, or more than 45 days (those with menstruation between 39-44 days not detailed)</li> <li>Use of allergy medicines</li> <li>Use of "hormonal drugs"</li> <li>Use of "pain killers"</li> <li>Not adherent to the treatment protocol</li> </ul>

At baseline, the two groups were similar with respect to age and other demographic features. VAS results are shown in Table 2. There was a statistically significant decrease in VAS scores over time for both groups ( $P < 0.001$ ), although the cinnamon group decreased more over time ( $P = 0.02$ ). Also, the VAS score was less in the cinnamon group after both the first cycle ( $P = 0.001$ ) and the second cycle ( $P = 0.002$ ). Adverse effects were not discussed.

#### ■ COMMENTARY

The choice of diagnosis is compelling, but the justification for studying cinnamon is not. In many cases with herbal medicine research, there are preclinical data or traditional use that steers researchers toward taking the next step in exploration, the randomized, controlled clinical trial. For "cinnamon," most of the research has been done on cassia cinnamon, a different species than what was used in this study. Furthermore, the cassia data seem most convincing for use in people with diabetes.<sup>4,5,6</sup> Their primary reason for studying cinnamon in PMS (more specifically, dysmenorrhea) was that it had not been studied for that before. It appears, then, that the researchers hit the jackpot and demonstrated a positive effect.

There were some "red flags" in the methodology of this study. Those participants who did not follow the treatment protocol apparently were excluded. A more accepted approach to lack of adherence would be to include them in the original randomized group, and then statistically analyze their outcome as intention-to-treat, as if they had completed the protocol. To exclude after randomization may create bias in the research results. Also, there was some sloppy writing or record keeping, or both: It is unclear whether women with menstruation duration of 39-44 days were included or excluded. In addition, women were included in the trial if, as per the VMS, they had mild or moderate dysmenorrhea, but the specifics of that scale were not discussed (although other scholarly articles provide that it ranges from 0-9, 0-3 on three different pain subsets). In addition, they recorded a "baseline" VAS score, but would this have been at the start of painful menstruation or some other time? It is unclear. This lack of attention to detail makes one wonder what else might have been overlooked or mistakenly addressed.

**Table 2: Menstrual Pain for the Cinnamon and Placebo Groups**

	Baseline	After Cycle 1	After Cycle 2
Placebo group	5.8	5.0	4.9
Cinnamon group	5.7	3.6 ( $P = 0.001$ compared to placebo group)	3.2 ( $P = 0.002$ compared to placebo group)
As per visual analog scale (from 0 to 10)			

Another important aspect to this paper is the proper identification of the intervention itself. More well-designed clinical trials investigating herbal medicines would have expanded on the herbal identification in the methods section. It was only in the Discussion section that a reference was made to the species name, *zeylanicum*, the not-so-common synonym of *C. verum*, one of the common spice species. The story is slightly confusing in that, unless expressly stated, spice cinnamon also could be cassia cinnamon, *C. aromaticum*, synonym *C. cassia*. Many clinical trials have been conducted on cassia cinnamon as referenced above. Does it matter? As with any herbal medicine, there are interspecies chemical nuances that can produce physiological effects. Clinicians can accurately base their recommendations only on this chemical specificity and the clinical trials that have been done on a particular species. Ideally, the researchers in this study would have provided information about the source of the cinnamon, as well as shown how the identification was made, either by laboratory techniques such as mass spectrometry, or, if the whole plant was available, corroborating the plant used in the study with a definitive authentication in an herbarium.

Looking past the methodological flaws, are the results clinically significant? Both groups improved over the two cycles studied, which the researchers mention could have been due to the "psychological support" (not detailed) offered during the study. Two cycles probably are not enough to conclude whether this is a trend or outlier; the next study should be longer. The treatment group showed an improvement in menstrual pain beyond the placebo group, a roughly 40% improvement during the course of the study. If these results hold up to more

EXECUTIVE EDITOR  
Leslie G. Coplin

EDITOR  
Jonathan Springston

EDITORIAL GROUP MANAGER  
Terrey L. Hatcher

SENIOR ACCREDITATIONS  
OFFICER  
Lee Landenberger

EDITOR  
David Kiefer, MD  
Clinical Assistant Professor, Department of  
Family Medicine, University of Wisconsin;  
Clinical Assistant Professor of Medicine,  
Arizona Center for Integrative Medicine,  
University of Arizona, Tucson

PEER REVIEWER  
Suhani Bora, MD  
Access Community Health Centers  
Madison, WI

EDITORIAL ADVISORY BOARD  
Donald Brown, ND  
Managing Director  
Natural Product Research Consultants  
Seattle

Russell H. Greenfield, MD  
Clinical Professor  
School of Medicine  
University of North Carolina  
Chapel Hill  
Visiting Assistant Professor  
University of Arizona College of Medicine  
Tucson

Dónal O'Mathúna, BS (Pharm), MA, PhD  
Senior Lecturer  
Ethics, Decision-Making & Evidence  
School of Nursing and Human Sciences  
Affiliated Scholar, Institute of Ethics  
Dublin City University, Dublin, Ireland

David Rakel, MD  
Associate Professor  
Department of Family Medicine  
Founder and Director, University of  
Wisconsin Integrative Medicine  
University of Wisconsin School of  
Medicine and Public Health, Madison

Craig Schneider, MD  
Director of Integrative Medicine  
Department of Family Medicine  
Maine Medical Center  
Portland, ME

rigorous analyses, this could be welcome relief to women suffering from PMS symptoms. With some of the mechanistic work cited by the researchers demonstrating cinnamon's anti-inflammatory effects, the physiological benefit is concordant with these results.

All told, the issues with this paper obscure the addition of a new tool to clinicians' treatments for dysmenorrhea. There is the hint of a plant anti-inflammatory alternative to the pharmaceuticals available for dysmenorrhea, but a new study, with fewer dropouts, an intention-to-treat analysis, and in-depth herbal identification, is necessary. ■

## REFERENCES

1. Hofmeister S, Bodden S. Premenstrual syndrome and premenstrual dysphoric disorder. *Am Fam Physician* 2016;94:236-240.
2. Chen P, Sun J, Ford P. Differentiation of the four species of cinnamons (*C. burmannii*, *C. verum*, *C. cassia*, and *C. loureiroi*) using a flow injection mass spectrometric (FIMS) fingerprinting method. *J Ag Food Chem* 2014;62: 2516-2521.
3. Aggarwal B, Yost D. *Healing Spices*. Sterling, NY; 2011.
4. Bi X, Lim J, Henry CJ. Spices in the management of diabetes mellitus. *Food Chem* 2017;217:281-293.
5. Medagama AB. The glycaemic outcomes of cinnamon, a review of the experimental evidence and clinical trials. *Nutr J* 2015;14:108.
6. Ríos JL, Francini F, Schinella GR. Natural products for the treatment of type 2 diabetes mellitus. *Planta Med* 2015;81:975-994.

## CME QUESTIONS

1. Which of the following is true regarding results from the meta-analysis on omega-3 polyunsaturated fatty acids (PUFAs) and anxiety?
  - a. Omega-3 PUFAs can be helpful in treating anxiety symptoms at doses of at least 2,000 mg/day, especially when there is a clinical diagnosis.
  - b. Omega-3 PUFAs can be helpful in treating anxiety disorders at doses of at least 2,000 mg/day, but not when the patient has comorbid medical conditions.
  - c. Omega-3 PUFAs can be helpful in treating anxiety symptoms at doses < 2,000 mg/day, but not when there are comorbid neurodegenerative conditions.
  - d. Omega-3 PUFAs can be helpful in treating anxiety disorders at doses of 2,000 to 4,000 mg/day, but not when there are comorbid neurodegenerative conditions.
2. Based on the study of the sage/rosemary/melissa tincture, which of the following statements is true about changes after two weeks?
  - a. Immediate word recall was significantly better in the treatment group in both age groups.
  - b. Delayed word recall was significantly better in the placebo group in both age groups.
  - c. Delayed word recall was significantly better in the treatment group in the younger age group.
  - d. Immediate word recall was significantly better in the treatment group in the older age group.
3. Which of the following statements is true regarding diet and depression based on the Lassale et al review and meta-analysis?
  - a. Compliance with almost any well-studied healthy diet lowers the risk of developing depressive symptoms, but not necessarily depressive disorder.
  - b. Lowering inflammatory potential of foods most likely is helpful in preventing depression (symptoms or disorder) in women, but the studies consistently show no effect in men.
  - c. There was an association between decreased risk of depressive symptoms and higher adherence to the Mediterranean diet in four longitudinal studies.
  - d. There was an association between decreased risk of depressive symptoms and lower adherence to the Mediterranean diet in four longitudinal studies.
4. Which of the following is true regarding the trial of cinnamon for dysmenorrhea?
  - a. Positive effects were seen in both of the menstrual cycles studied.
  - b. Placebo and treatment groups had similar improvements over time.
  - c. The dose of cinnamon used was 1,500 mg daily.
  - d. The species used was cassia cinnamon (*Cinnamomum cassia*).

## [IN FUTURE ISSUES]

Unapproved Ingredients  
in Dietary Supplements

Blueberries and  
Dementia

Social Media Use  
and Adolescent  
Mental Health

Tai Chi and Falls  
in the Elderly

Interested in reprints or posting an article to your company's site? There are numerous opportunities for you to leverage editorial recognition for the benefit of your brand.  
Call us: (800) 688-2421  
Email us: reprints@reliamedia.com

For pricing on group discounts, multiple copies, site licenses, or electronic distribution, please contact our Group Account Managers at:

Phone: (866) 213-0844  
Email: groups@reliamedia.com

To reproduce any part of Relias Media newsletters for educational purposes, please contact:

The Copyright Clearance Center for permission  
Email: info@copyright.com  
Phone: (978) 750-8400