

Integrative Medicine

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the latest developments in integrative therapies [ALERT]

DIET

ABSTRACT & COMMENTARY

Dairy Intake and Risk of Parkinson's Disease

By Allison Becker, ND, LAc

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

SYNOPSIS: Frequent consumption of dairy products is associated with a modest increased risk of Parkinson's disease (PD) in women and men. In addition, intake of high-fat dairy is associated with decreased risk of PD.

SOURCE: Hughes KC, Gao X, Kim IY, et al. Intake of dairy foods and risk of Parkinson's disease, *Neurology* 2017;89:46-52.

Parkinson's disease (PD) is a long-term degenerative neurological condition that affects 6.2 million people worldwide.^{1,2} The aim of any therapy for the treatment of PD, albeit drug, diet, exercise, surgery, or acupuncture, is to slow the inevitable progression of the disease and minimize motor symptoms. As there is no cure for PD, identifying factors contributing to the development of PD and focusing on prevention is of utmost importance, particularly in those with a family history of the disease.

Dairy products are consumed widely and would be an important modifiable risk factor for this disease. Other researchers have found an association between

dairy intake and the risk of PD. Hughes et al investigated two questions: whether certain dairy foods or nutrients present in dairy foods are driving this association and whether there are differences between men and women. PD affects men more than women in a 3:2 ratio.³ Hughes et al combined data from two large prospective cohort studies: the Nurses' Health Study (NHS; n = 80,736) and the Health Professionals Follow-up Study (HPFS; n = 48,610), with a total of 26 and 24 years of follow-up, respectively. Both studies collected dietary intake with a food frequency questionnaire completed every two years. Hughes et al presented data from both studies for an additional 12 years of follow-up, with a total of 1,036 incident cases of PD.

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Summary Points

- Consumption of more than three servings per day of low-fat dairy foods, including skim and low-fat milk, sherbet, and frozen yogurt, was associated with an increased risk of Parkinson's disease.
- A significant linear trend for decreased risk was associated with a greater intake of high-fat dairy.
- Men and women have similar risks, increased or decreased, of Parkinson's disease, based on these variations in milk intake.

The NHS began in 1976 when female registered nurses aged 30 to 55 years responded to a questionnaire about their medical history and health-related behaviors. The HPFS also began in 1976 when male health professionals aged 40 to 75 responded to a similar questionnaire. Individuals in the current analysis were excluded if they had an excessive or insufficient caloric intake (< 660 or > 3,500 kcal/day for women and < 800 or > 4,200 kcal/day for men), had a previous diagnosis of PD, or had missing baseline dietary information. Multivariable models were adjusted for pack-years of smoking, coffee intake, body mass index, physical activity, alcohol intake, and total energy intake.

In the NHS study, diet was assessed at baseline in 1984, 1986, and every four years thereafter. In the HPFS study, diet was assessed initially in 1986 (baseline) and every four years thereafter. Participants were asked to report each portion of food from never to more than six times per day. Dairy intake was separated into the following categories: total dairy and individual dairy products including skim or low-fat milk, whole milk, cream, sour cream, cream cheese, cottage cheese, low-fat cheese, other cheese, ice cream, yogurt, sherbet, frozen yogurt, butter, and margarine.

Only patients with confirmed cases of PD were included in this analysis. These cases were confirmed if the physician considered the PD diagnosis definite or probable, the medical record included the final diagnosis of PD by a neurologist, or the medical record indicated the presence of at least two of the three cardinal signs of PD (resting tremor,

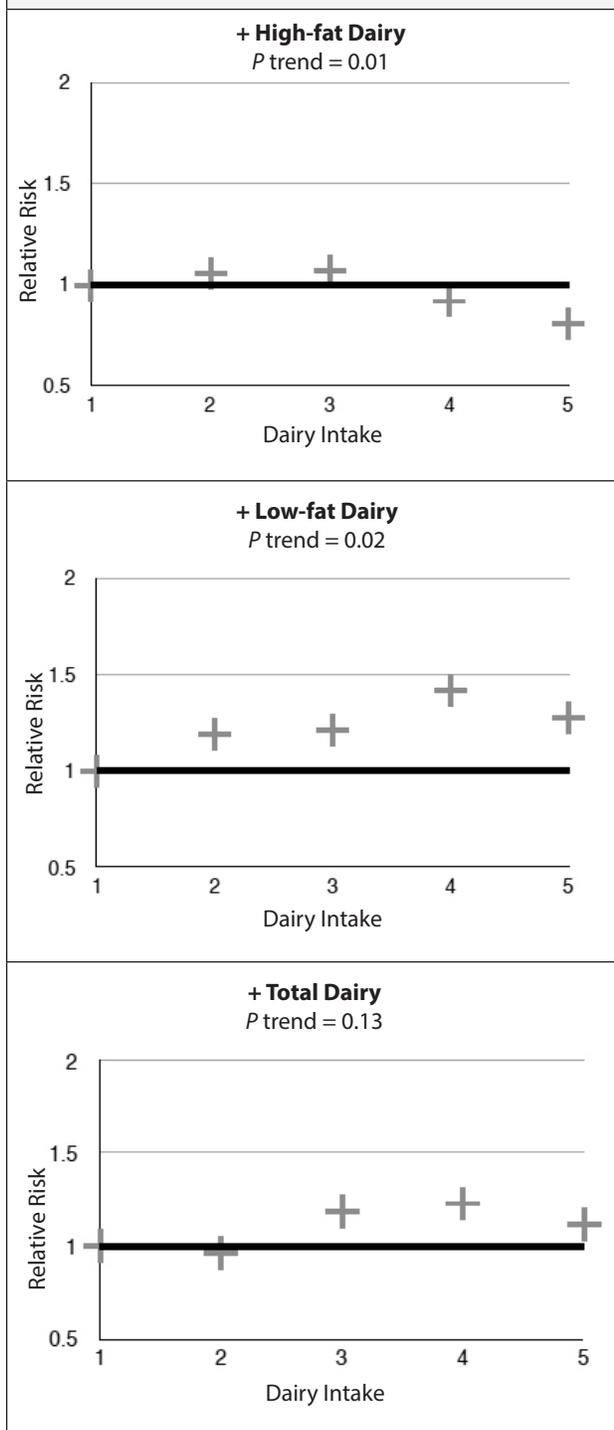
rigidity, bradykinesia) in the absence of evidence for another diagnosis.

A lagged analysis was conducted that excluded the first four years of follow-up in each cohort. This was to address the possibility of participants who may have been experiencing PD symptoms at the time of the questionnaire changing their dietary habits. Often, people will improve their dietary habits when diagnosed with a chronic disease. This lagged analysis was intended to reduce this confounding variable. Overall, results of the lagged analysis were similar to those of the main analysis.

The authors included 554 PD cases in men and 482 PD cases in women. When comparing people who ate three or more dairy foods per day to those who ate less than one per day, the authors found no association with PD risk (hazard ratio [HR] 1.16; 95% confidence interval [CI], 0.92-1.48; *P* trend = 0.19). Interestingly, for low-fat dairy foods, there was an elevated risk for PD when the same high-intake vs. low-intake comparison was made (HR, 1.34; 95% CI, 1.01-1.79; *P* trend = 0.04). This association mostly seemed to be due to intake of skim or low-fat milk products, even more specifically sherbet/frozen yogurt. In contrast, high-fat dairy tended to be associated with a lower risk of PD development. (See Figure 1.) All of these results were similar in men and women.

The authors conducted further analysis for specific nutrients found in dairy products, including protein, calcium, vitamin D, and lactose. Neither total intake nor intake of these nutrients from dairy was significantly associated with

Figure 1: Association of Dairy With Parkinson's Disease



PD risk. A sensitivity analysis was conducted by restricting the case definition to definite PD, by analyzing for nonsmokers, and by censoring participants at age 85 years because of the increased difficulty in diagnosing PD at older ages. The results were similar to the main analysis. These results for milk intake were pooled with three previously published studies with a total of 1,725 PD

cases and total dairy results with one previously published study. The pooled relative risk for total milk intake was 1.56 and the pooled relative risk for total dairy intake was 1.27.

COMMENTARY

This analysis, the largest of its kind to date, yields useful guidance for clinicians. Most of the contributing factors to the development of PD are largely unknown. As with many other diseases, PD appears to be a combination of both inherited and environmental factors.³ The information in this analysis is particularly significant for individuals with a relative with a family history of PD. About 15% of people with PD have a first-degree relative with the disease.⁴ The genetic influence on the development of PD is likely due to susceptibility to negative environmental effects. However, clinicians should recognize those with a family history of PD and teach those patients about the association between frequent consumption of low-fat dairy and increased PD risk. Daily consumption of more than three servings of low-fat dairy products, especially skim and low-fat milk, frozen yogurt, and sherbet, significantly increased the risk of PD. This risk was reversed with the consumption of high-fat dairy. This effect was seen in men and women equally. The authors of previous studies on dairy and PD risk did not evaluate specific types of dairy. This current analysis yields unique information that can be used clinically to educate patients.

One mechanism proposed to explain the association between certain dairy products and the increased risk of PD is the “anti-uricemic effect” of dairy proteins, which refers to dairy effectively reducing serum urate levels.^{5,6} Reducing serum urate levels may be a problem for those PD patients. Studies show urate actually may be protective against PD.^{7,8} Specifically, consuming low-fat dairy, not high-fat dairy, reduces the risk of gout, demonstrating the particularly anti-uricemic effect of low-fat dairy.⁹ Full-fat dairy is high in saturated fat, which may counteract the anti-uricemic effect of the proteins in full-fat milk. This may explain why full-fat dairy decreases the risk of PD. Further research is needed to elucidate the mechanisms involved in this association.

Lastly, in particular, clinicians should pay attention to patients both with early signs of PD and with a genetic susceptibility for developing PD. Inquire into the patients’ dairy intake and educate patients about the increased risk of PD development with frequent low-fat dairy intake as well as a decreased risk with consumption of high-fat dairy. ■

REFERENCES

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388:1545–1602.
2. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1459–1544.
3. Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015;386:896–912.
4. Samii A, Nutt JG, Ransom BR. Parkinson's disease. *Lancet* 2004;363:1783–1793.
5. Garrel DR, Verdy M, PetitClerc C, et al. Milk and soy-protein ingestion: Acute effect on serum uric acid concentration. *Am J Clin Nutr* 1991;53:665–669.
6. Dalbeth N, Wong S, Gamble GD, et al. Acute effect of milk on serum urate concentrations: A randomized controlled crossover trial. *Ann Rheum Dis* 2010;69:1677–1682.
7. Gao X, O'Reilly EJ, Schwarzschild MA, Ascherio A. Prospective study of plasma urate and risk of Parkinson's disease in men and women. *Neurology* 2016;86:520–526.
8. Weiskopf MG, O'Reilly E, Chen H, et al. Plasma urate and risk of Parkinson's disease. *Am J Epidemiol* 2007;166:561–567.
9. Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* 2004;350:1093–1103.

EXERCISE

ABSTRACT & COMMENTARY

Tai Chi or Aerobics: Which Is Better for Fibromyalgia?

By *Ellen Feldman, MD*

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

SYNOPSIS: In this randomized, controlled trial, researchers found that tai chi shows equal or greater effect than aerobic exercise for addressing symptoms of fibromyalgia, and that more effect is obtained with longer duration of tai chi practice.

SOURCE: Wang C, Schmid CH, Fielding RA, et al. Effect of tai chi versus aerobic exercise for fibromyalgia: Comparative effectiveness randomized controlled trial. *BMJ* 2018;360:k851

Chronic pain is one of the most frequent presenting symptoms in primary care clinical practice. Because of the difficulty of successful treatment, it is also one of the most frustrating conditions for providers to address.¹ According to the International Association for the Study of Pain, 20% of adults worldwide experience chronic pain; the physical, emotional, and financial implications of this often-debilitating health problem affect lives on many levels — from individual patients to families and to society as a whole.²

Fibromyalgia (FM) is a multifaceted disorder and one of the main causes of chronic widespread pain. A hallmark of this disorder is chronic, diffuse musculoskeletal pain; other associated symptoms include disordered sleep, mood changes, and concentration difficulties. Some researchers and clinicians believe FM is a distinct condition, while others place it as part of a spectrum of chronic widespread pain, and still others consider the pain symptoms as part of a psychiatric disorder. Estimates of worldwide prevalence of FM (from 26 epidemiologic studies) are 2.7%, with a higher prevalence in women and in those > 50 years of age.^{3,4}

Summary Points

- Wang et al evaluated the relative efficacy of tai chi vs. aerobic exercise in managing fibromyalgia and investigated optimal frequency and duration of tai chi practice.
- Subjects were placed in one of five groups: One group performed aerobic exercise twice weekly for 24 weeks and four Yang-style tai chi groups practiced at several specified durations (once or twice weekly and 12 or 24 weeks).
- All treatment groups had improved fibromyalgia impact questionnaire scores. The average scores of the combined tai chi groups showed more significant improvement than the aerobic group; when matched for intensity and duration of intervention, the tai chi group scores were even more significant.
- Within the tai chi groups, the 24-week group had greater improvement than the 12-week group.

Table 1: Differences in Outcome Scores

		FIQR score	Anxiety	Global assessment score	Pittsburgh Sleep Quality Index	Six-minute walk test
24-week aerobic exercise 2/week vs. 24-week tai chi 2/week	Week 12	10.9 (P = 0.005)	1.7 (P = 0.02)	0.3 (<i>P = 0.57</i>)	0.6 (<i>P = 0.37</i>)	-3.0 (<i>P = 0.45</i>)
	Week 24	16.2 (P < 0.001)	2.1 (P = 0.008)	1.6 (P = 0.0006)	1.0 (<i>P = 0.22</i>)	-1.0 (<i>P = 0.94</i>)
	Week 52	11.1 (P = 0.01)	1.6 (P = 0.04)	1.5 (P = 0.008)	0.9 (<i>P = 0.26</i>)	22.6 (<i>P = 0.27</i>)
Tai chi 12 weeks vs. 24 weeks	Week 12	-2.7 (<i>P = 0.44</i>)	0.0 (<i>P = 0.93</i>)	-0.6 (<i>P = 0.12</i>)	0.0 (<i>P = 0.99</i>)	-10.7 (<i>P = 0.31</i>)
	Week 24	9.6 (P = 0.007)	0.4 (<i>P = 0.55</i>)	0.7 (<i>P = 0.12</i>)	1.0 (<i>P = 0.16</i>)	-9.3 (<i>P = 0.39</i>)
	Week 52	5.8 (<i>P = 5.1</i>)	-0.6 (<i>P = 0.41</i>)	0.6 (<i>P = 0.17</i>)	-0.9 (<i>P = 0.24</i>)	17.1 (<i>P = 0.27</i>)
Total tai chi vs. aerobic exercise	Week 12	5.4 (P = 0.03)	1.2 (P = 0.003)	0.6 (P = 0.03)	0.1 (<i>P = 0.78</i>)	6.8 (<i>P = 0.37</i>)
	Week 24	5.5 (P = 0.03)	1.2 (P = 0.006)	0.9 (P = 0.005)	0.3 (<i>P = 0.49</i>)	6.0 (<i>P = 0.45</i>)
	Week 52	2.7 (<i>P = 0.29</i>)	1.3 (P = 0.009)	0.8 (P = 0.01)	0.6 (<i>P = 0.24</i>)	12.5 (<i>P = 0.24</i>)

Bold *P* values are statistically significant.

There is no known cure for FM. Pharmaceutical agents (mostly analgesics) have limited long-term benefit. On the other hand, aerobic exercise is an accepted standard of care in managing this disorder, but is a difficult sell for many patients who report that exercising while in pain is prohibitive.^{3,4}

Tai chi is a traditional Chinese systemic exercise program known for improving balance, flexibility, and endurance. Wang et al reported that several promising small-scale studies examined the effectiveness of tai chi in management of FM prior to this study. Given there were no previous studies comparing tai chi to aerobic exercise in FM patients and no studies regarding optimal “dose” (frequency and duration) of tai chi intervention, Wang et al designed their investigation to elicit this information. To standardize the tai chi intervention, the treatment protocol restricted the tai chi practiced to the Yang type and rotated one set of three instructors among the tai chi groups.

Two hundred and twenty-six adults with FM qualified for this study and were randomized into one of five treatment arms. All were followed up to 52 weeks. The protocol involved six cycles of intervention (12 or 24 weeks each) to control for seasonable variation in response and allow instructors to rotate among groups. Exclusion criteria for participation included recent experience with tai

chi, some medical comorbid conditions, and cognitive impairments.

One treatment arm participated in a supervised, hour-long group aerobic exercise program twice weekly for 24 weeks. The other four arms were all tai chi interventions — once or twice weekly and either 12 or 24 weeks. All participants received an additional educational component and encouragement to practice at home. Given this was a head-to-head comparison between the two interventions as well as an inter-group comparison within the tai chi arms, no control or usual-care group was defined.

There were some adverse events reported by participants during this study; none were serious or directly stemmed from any of the interventions.

SELECTED RESULTS

Every group had improvement in Revised Fibromyalgia Impact Questionnaire (FIQR) scores. (See Table 1.) However, when comparing the FIQR score differences between interventions, tai chi group scores were lowered more significantly than aerobic exercise scores. For example, at 24 weeks, when comparing aerobic exercise and tai chi at matched rate and frequency of intervention, the difference between the scores was 16.2 (*P* < 0.001).

Secondary outcome results included anxiety and global assessment score, each of which improved more with a tai chi intervention than with aerobic exercise, but with varying degrees of significance. For example, at the same 24-week mark in the groups matched for intensity and frequency of intervention, anxiety score differences were 2.1 favoring the tai chi intervention ($P = 0.008$) and global assessment score differences were 1.6 ($P = 0.0006$), also favoring the tai chi arm.

In all categories, the significant differences in outcome measures at 24-week follow-up attenuated at 52 weeks, and in some cases lost significant difference completely at the 52-week mark. This was particularly noticeable when comparing the combined average FIQR score of the tai chi interventions with aerobic exercise. At week 24, the difference in scores was 5.5 ($P = 0.03$) favoring the tai chi arm, but at the 52-week follow-up, the score difference was no longer significant.

Attendance was higher in the tai chi groups as a whole. The tai chi groups combined had a 62% attendance rate compared with 40% attendance rate in the aerobic group. Wang et al applied several statistical measures to control and account for this difference.

Some secondary outcome measures, including sleep quality and a six-minute walk test score, did not show significant differences between interventions. Likewise, although every group showed a reduction in the use of analgesics, there was no significant difference in this measure among the interventions. There were no significant differences found in outcome measures when tai chi once weekly was compared to twice weekly.

■ COMMENTARY

Tai chi is an ancient Chinese martial art with a long-standing role in Chinese traditional medicine.⁵ In discussing tai chi in 2017, Peter Wayne, research director of the Osher Center for Integrative Medicine in Boston, remarked, “I think of it as meditation on wheels. You’re getting all the cognitive pieces you might get from meditation — mental clarity and focus and positive thoughts and lower stress — but you’re also getting physical exercise.”⁶

There are five major styles of tai chi. The Yang style is the most popular worldwide, and most likely to be the type of tai chi seen practiced in parks or large group settings. Movements tend to be slow, steady, and deliberate as opposed to the older Chen style, which is characterized by more

energetic and faster movements interspersed with slower movements. On the other hand, the Sun style concentrates on internal movements and stillness.⁵

One of the strengths of the Wang et al study is the standardization of the type of tai chi taught to Yang style and the use of three instructors rotating among all groups. Past investigations of tai chi have suffered in credibility because of lack of these controls. Additional strengths are the relatively long-term follow-up to 52 weeks, as well as the head-to-head testing of two different “doses” or frequencies of tai chi weekly and two different durations (12 or 24 weeks.)

In essence, Wang et al studied two non-pharmaceutical approaches to manage FM and found tai chi weekly (for 24 weeks) delivered a more robust intervention than aerobic exercise delivered at the same frequency and duration. According to Wang et al, the minimally clinical noticeable difference in FIQR scores is 8.1. Thus, the differences at weeks 12, 24, and 52 (10.9, 16.2, and 11.1, respectively) between FIQR scores when comparing tai chi and aerobic exercise matched for rate and frequency should hold clinical significance. However, many of the other FIQR differences among the compared groups were < 8.1 and while significant, may not hold clinical relevance.

By week 52, the significance of the differences between most groups had diminished. This may mean that the tai chi intervention needs to be maintained for a longer period, but there are no direct data to support this without longer-term studies. The drop-in use of analgesics from all interventions is a notable caveat for providers managing patients with FM.

It is interesting that attendance rate for the tai chi classes was higher than for the aerobic exercise classes. Wang et al explained that this could mean that patients with FM are more likely to practice and continue a tai chi intervention as opposed to aerobic exercise. However, this attendance difference could also have affected the results, although there were statistical measures, including intention-to-treat analysis, to control for this possibility.

It may be difficult to find a high-quality tai chi program in more isolated communities. Wang et al studied on-site group tai chi instruction with home practice. Future studies with remote or virtual tai chi instruction would be useful to understand if this individual modality is also effective in easing

the symptoms of FM. There is no obvious path in the Wang et al study to account for the effect of group dynamics on interventions in addressing FM symptoms, and it may be that the group setting itself accounts for a portion of the response rate seen with both types of interventions.

Clearly, future studies aimed at understanding the nuances of response to specific mind-body and exercise interventions are needed. Perhaps there are predisposing factors, such as age, gender, body mass index, or even socioeconomic factors, that allow prediction of response to specific interventions; knowing such factors can lead to development of individually tailored management programs for patients with FM.

The Wang et al study gives providers exciting and encouraging news for patients with FM. Notably, there were few adverse effects in the study and none related specifically to tai chi. Telling patients that tai chi practice may help in management of FM symptoms, reduce their dependence or use of analgesics, and positively affect quality of life can give hope to those who feel current efforts and

interventions are less than adequate. The ability to provide concrete information, recommending a tai chi dose of one hour of practice once weekly for 12 weeks with increased benefits after 24 weeks, may be reassuring and conducive to incorporating this ancient Chinese form of exercise into a 21st century multimodality treatment strategy aimed at control of FM. ■

REFERENCES

1. Matthias MS, Parpart A, Nyland KA, et al. The patient-provider relationship in chronic pain care: Provider's perspectives. *Pain Med* 2010;11:1688-1697.
2. Goldberg DS, McGee SJ. Pain as a global public health priority. *BMC Public Health* 2011;11:770.
3. Centers for Disease Control and Prevention. Fibromyalgia. Available at: <https://www.cdc.gov/arthritis/basics/fibromyalgia.htm>. Accessed April 10, 2018.
4. Queiroz LP. Worldwide epidemiology of fibromyalgia. *Curr Pain Headache Rep* 2013;17:356.
5. Beginners Tai Chi. Tai Chi History: An Overview. Available at: <https://www.beginnerstaichi.com/tai-chi-history.html>. Accessed April 11, 2018.
6. Osher Center for Integrative Medicine. Harvard Medical School and Brigham and Women's Hospital. Peter Wayne, featured in TIME Health on the benefits of tai chi. Available at: <https://oshercenter.org/2017/05/03/tai-chi-compared-to-crossfit/>. Accessed April 9, 2018.

MIND-BODY MEDICINE

ABSTRACT & COMMENTARY

Mindfulness-based Intervention in Patients With Generalized Anxiety Disorder

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Mrs. Benedicto reports no financial relationship relevant to this field of study.

SYNOPSIS: Reductions in stress markers for patients with generalized anxiety disorder were found using mindfulness-based stress reduction intervention.

SOURCE: Hoge EA, Bui E, Palitz SA, et al. The effect of mindfulness meditation on biological acute stress responses in generalized anxiety disorder. *Psychiatry Res* 2018;262:328-332.

Generalized anxiety disorder (GAD) is a debilitating condition that is the most frequent anxiety disorder in primary care.¹ Patients with a GAD diagnosis often complain of repeated and chronic worry, sleeplessness, and irritability. Other symptoms include fatigue, muscle aches, nervousness, and difficulty concentrating. Mindfulness-based interventions increasingly are used in psychiatry, with the most benefits found with anxiety and depression.² Most studies have focused on subjective conclusions from participants, so more randomized and adequately controlled trials are needed.

Summary Points

- Mindfulness-based stress reduction (MBSR) may be valuable for people who have generalized anxiety disorder, for both mental support and positive physical health outcomes.
- Participants in a MBSR intervention group saw a decrease in adrenocorticotrophic hormone, interleukin-6, and tumor necrosis factor-alpha.

Table 1: AUC in MBSR and SME Hormone Changes

	Pre-cortisol AUC	Post-cortisol AUC	Change Cortisol
MBSR	913	760	-152
SME	1,040	951	-89
	ACTH AUC	ACTH AUC	Change ACTH
MBSR	1,979	1,688	-290
SME	2,148	2,348	200

AUC: area under the curve; ACTH: adrenocorticotropic hormone; MBSR: mindfulness-based stress reduction; SME: stress management education.

Mindfulness-based stress reduction (MBSR) was developed at the University of Massachusetts Medical Center by Jon Kabat-Zinn in the 1970s. The practice involves eight weeks of mindfulness meditation, body scanning, and hatha yoga. MBSR is described as a group program that focuses on the progressive acquisition of mindful awareness.³

To educate patients properly, clinicians need to know more about mindfulness-based practices and how they can be used appropriately for GAD. Hoge et al studied a group of 70 participants with GAD who were randomized to either an eight-week MBSR group or to an attention control class, called stress management education (SME). Other researchers have looked at self-reported and subjective findings from participants. The authors of this study expanded on this prior work by measuring inflammatory biomarker and stress hormone changes from chronic or repeated stress in patients with GAD.

Inflammatory markers and stress hormones fluctuate with chronic or repeated stress. These same blood markers are associated with the risk of developing cardiovascular disease and metabolic syndrome.^{4,5} Research showed that patients with GAD and other chronically stressed populations have an exaggerated neuroendocrine response to the Trier social stress test (TSST) compared to healthy controls.⁶ The TSST is a well-validated, widely used, lab-based model of psychological stress.⁷ Researchers hypothesized that MBSR would reduce this exaggerated response to acute stress observed in people with GAD as demonstrated by decreased biomarker levels. In a 2013 study, Hoge et al measured only self-reported and subjective changes in people with GAD. They took a subset of participants with GAD and tested changes in biomarkers using MBSR and SME in a randomized, controlled approach.⁸ Clinical anxiety ratings dropped with MBSR in most measures during the

study from 2013.⁸ The researchers examined the laboratory results from a group of patients from this study for hormones and inflammatory marker changes. The hormones studied were cortisol and adrenocorticotropic hormone (ACTH) and markers of inflammation were tumor necrosis factor (TNF)-alpha and interleukin (IL)-6. In 2013, they hypothesized that decreasing biological stress responses may improve overall cardiovascular and metabolic health, although that was not measured for this study.

The initial 2013 study included individuals older than 18 years of age who were diagnosed with GAD using the DSM-IV. They were randomized to a modified MBSR or SME group. Prior to the start of the intervention groups, participants completed the TSST and all blood testing. After the eight-week intervention, they returned for the second TSST. The researchers took several measures for the second TSST, including new room and new administrators, to lower potential stress habituation and improve study rigor.

The MBSR intervention was shortened from the original protocol. Classes were shortened from 2.5 to two hours, the day-long retreat was only four hours, and homework was only 20 minutes instead of the usual 45 minutes.

Seventy-nine participants completed the original 2013 study; 72 were eligible for the blood tests and were not analyzed by intention-to-treat. Some data were missing because of plasma quality and catheter failure, so the final sample sizes with all three time points for each biomarker were: n = 67 for ACTH, n = 68 for cortisol, n = 65 for TNF-alpha, and n = 62 for IL-6.

Calculations were made from the biomarkers during stress pre- and post-treatment using an area under the curve (AUC) for ACTH, TNF-alpha,

cortisol, and IL-6 with +5 as the baseline blood level. The AUC for hormone and inflammatory levels before and after eight weeks of treatment are shown in Table 1. There were no significant differences in gender, age, or race distribution. Of the 72 participants eligible for blood tests and who were not analyzed by intention-to-treat, three dropped out from the MBSR group and 11 dropped out from the SME group.

■ COMMENTARY

As Hoge et al stated, “The value of an intervention that can improve resilience to psychological stress in this population cannot be over-estimated.”

According to the American Psychological Association, psychological resilience is the process of adapting well when faced with adversity, trauma, tragedy, threats, or significant sources of stress.⁹ These findings help elucidate the benefits of using MBSR to gain resilience in the face of chronic or repeated stress for patients with GAD.

According to the National Institutes of Mental Health, in 2007, 19.1% of U.S. adults had an anxiety disorder diagnosis. An estimated 31.1% of U.S. adults suffer from an anxiety disorder at some point in their lives.¹⁰ Although mindfulness-based programs are low-cost treatment interventions, practitioners and facilitators may not be readily available in a clinic setting. Also, since not covered by insurance, access may be limited for patients.

Hoge et al found MBSR beneficial to participants with GAD, but there were multiple limitations. First, the researchers used laboratory stress vs. real-life stress as the basis for the study. Although previous studies have shown improved laboratory stress coping directly linked to improved mental health outcomes, more studies with real-life stress would increase the scientific rigor of these outcomes.¹¹

The original study included self-reporting and subjective responses, which often can be unreliable. Previous researchers have found a correlation between stress hormones and subjective stress and self-reporting in only about 25% of studies.¹² Fortunately, this extension of the original study measured lab markers that allow for objective results.

The population was quite small, with a total of 70 individuals, so larger-scale studies would be welcomed. The exclusion criteria, which included a lifetime of psychotic disorder, intellectual disability, organic medical disorders, bipolar disorders, obsessive-compulsive disorder, post-traumatic

stress disorder, current or past alcohol or substance abuse or dependence, suicidal behaviors, and those in psychotherapy for GAD, may have limited their generalizability of the outcomes.

Also, MBSR is an intensive program that requires eight weeks of continuous involvement, including two hours or more each day, plus a day of retreat, and additional yoga and meditation. Researchers shortened the amount of time that individuals would be required to participate, but it is still a long-time commitment for most patients seen in a typical clinical setting.

[In an ideal clinical scenario, mindfulness-based stress reduction would be a continuous offering, available to patients with set cohorts and schedules to deliver the program. Virtually any intervention that decreases the acute stress response and increases the relaxation response is going to be valuable in this vulnerable population.]

Allostatic load is the physiological wear-and-tear on the body from repeated and/or chronic stress.¹³ Studies have shown that positive social experiences are associated with lower allostatic load, but there is no discussion about the benefits of social support from individuals in the MBSR group. Community and social support affect biological systems that have played a part in positive health outcomes.¹⁴ The researchers controlled this non-specific effect of social support in the SME group.

Introducing a mindfulness-based practice to patients in most clinic settings often is met with uncertainty, sometimes on behalf of both the patient and the clinician. This study is promising, but difficult to replicate because of the extensive time commitment that MBSR requires. In an ideal clinical scenario, MBSR would be a continuous offering, available to patients with set cohorts and schedules to deliver the program. Virtually any intervention that decreases the acute stress response and increases the relaxation response is going to be valuable within this vulnerable

population. Future work should expand on the number of participants as well as integrate real-life stress as part of the research. Although presented as a hypothesis, more research and more thorough studies showing how MBSR is linked to improving cardiovascular and metabolic health outcomes would be beneficial. A more accessible, less time-consuming intervention that succeeds at decreasing inflammatory markers and stress hormones also would have value and would add to the emerging evidence surrounding mindfulness-based tools and anxiety. ■

REFERENCES

1. Wittchen HU. Generalized anxiety disorder: Prevalence, burden and cost to society. *Depress Anxiety* 2002;16:162-171.
2. Groves P. Mindfulness in psychiatry — where are we now? *BJPsych Bull* 2018;40:289-292.
3. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits: A meta-analysis. *J Psychosom Res* 2004;57:35-43.
4. Chrousos GP. The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of metabolic syndrome: Neuroendocrine and target tissue-related causes. *Int J Obes Relat Metab Disord* 2000;24(Suppl 2):S50-S55.
5. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000;101:1767-1772.
6. Gerra G, Zaimovic A, Zambelli U, et al. Neuroendocrine responses to psychological stress in adolescents with anxiety disorder. *Neuropsychobiology* 2000;42:82-92.
7. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier social stress test' — a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 1993;28:76-81.
8. Hoge EA, Bui E, Marques L, et al. Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: Effects on anxiety and stress reactivity. *J Clin Psychiatry* 2013;74:786-792.
9. American Psychological Association. The Road to Resilience. Available at: <http://www.apa.org/helpcenter/road-resilience.aspx>. Accessed March 23, 2018.
10. Harvard Medical School, 2007. National Comorbidity Survey (NCS). Data Table 2: 12-month prevalence DSM-IV/WMH-CIDI disorders by sex and cohort. Available at: <https://www.hcp.med.harvard.edu/ncs/index.php>. Accessed March 20, 2018.
11. Aschbacher K, Epel E, Wolkowitz OM, et al. Maintenance of a positive outlook during acute stress protects against inflammatory reactivity and future depressive symptoms. *Brain Behav Immun* 2012;26:346-352.
12. Campbell J, Ehler U. Acute psychological stress: Does the emotional stress response correspond with psychological responses? *Psychoneuroendocrinology* 2012;37:1111-1134.
13. Robertson T, Beveridge G, Bromley C. Allostatic load as a predictor of all-cause and cause-specific mortality in the general population: Evidence from the Scottish Health Survey. *PLoS One* 2017;12:e0183297.
14. Seeman TE, Singer BH, Ryff CD, et al. Social relationships, gender and allostatic load across two age cohorts. *Psychosom Med* 2002;64:395-406.

OPIOIDS

SHORT REPORT

Saffron as Adjunctive Therapy for Opioid Withdrawal

By David Kiefer, MD

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

SYNOPSIS: A small, poorly designed study hints at some adjunctive treatment benefit for saffron powder in people weaning off narcotic medications.

SOURCE: Nemat Shahi M, Asadi A, Behnam Talab E, Nemat Shahi M. The impact of saffron on symptoms of withdrawal syndrome in patients undergoing maintenance treatment for opioid addiction in Sabzevar Parish in 2017. *Adv Med* 2017;2017:1079132. doi: 10.1155/2017/1079132. Epub 2017 Nov 21.

Saffron is the quintessential flavor in the Mediterranean rice and seafood dish called paella, but the researchers of this clinical trial moved beyond dinner. They used an extract of the spice as adjunctive therapy in people trying to wean themselves off narcotic medications.

The topic is compelling, but the prose and methodology made it a challenge to tease out results and draw firm conclusions about the intervention.

Summary Point

- In conjunction with decreasing doses of methadone, patients who consumed saffron powder for eight weeks had decreased opioid withdrawal symptoms when compared to placebo.

Patients of an addiction treatment center in Sabzevar parish, Iran, were selected randomly to participate in this intervention, and then randomly assigned to either saffron capsules (30 mg of saffron powder per capsule) or placebo capsules. The authors stated once that this intervention was offered once weekly, but it is unclear how many patients were in each arm of the clinical trial. They only mentioned that “44 clients” participated in this study in the abstract. Further, they stated that if the study participants “... did not have the ability to continue the process of intervention, they would be excluded from the research.” This seems to indicate that an important methodological characteristic, intention-to-treat analysis, was not at play.

Regarding inclusion criteria, the patients had to be stable on maintenance methadone dosing without “physical and mental symptoms.” Patients presented to the clinic once weekly, at which time their methadone dosing was decreased by 5 mg, and the week’s worth of saffron or placebo capsules (one capsule weekly) were prescribed. Telephone calls (unclear how often) monitored the patients for withdrawal symptoms and treatment adherence. Baseline methadone dose was not described, nor was the reason for maintenance methadone treatment.

The authors followed withdrawal symptoms, including loss of appetite, diarrhea, rhinorrhea, myalgia, and “temptation.” Over the eight-week intervention period, the percentage of patients experiencing each of these symptoms was displayed on graphs for the saffron and placebo groups. Numbers on the graphs also were included, which might represent the number of patients reporting each of those symptoms, but that is merely conjecture; it was not labeled as such. A “downward trend” in loss of appetite, diarrhea, and temptation; a “lagging downward trend” for rhinorrhea; and a “serious downward trend” for myalgia were described for the saffron group. People in the placebo group either had stable symptoms or increased symptoms over the study period. No statistical analyses were offered other than in the abstract with this statement: “The results showed that the use of saffron and methadone alleviated the symptoms of withdrawal syndrome ($P < 0.001$).”

The opioid crisis is just that, a crisis. The desperate attempts to establish evidence-based adjunctive therapies for opioid withdrawal symptoms probably explain why this article was published in an

open-access journal, when, mostly because of serious methodological flaws, it should not have been published. The title and abstract likely raise the hopes of any clinicians working in this field, and, indeed, saffron might be the correct herbal medicine to have been chosen to fill this public health need. Saffron has a relevant mechanism of action, with centrally acting neurotransmitter effects that could address comorbid psychological conditions in people with chronic pain or narcotic addiction.¹ The authors also mentioned that saffron, as with methadone, affects the reuptake of serotonin, but no references were provided for this statement.

[Why mention a study like this, given its marginal design and results? Mostly to help saffron appear on our clinical radar as we creatively approach the opioid crisis and extend beyond the antidepressant use of this herbal medicine.]

In addition, prior clinical trials have used 30 mg daily (or 15 mg twice daily), so the participants in this study either were under-dosed markedly, or there was an error in the reporting of the data.

Do the results of this study change our management of chronic pain, opioid addiction, and related conditions? Not yet. Tried and true methods of integrative, individualized, team-based care are still the best approach. Why mention a study like this, given its marginal design and results? Mostly to help saffron appear on our clinical radar as we creatively approach the opioid crisis and extend beyond the antidepressant use of this herbal medicine. It’s unclear whether saffron is efficacious as the authors of this study claim, but it seems to represent the beginning of unique therapies being studied to help this demographic in diverse and interesting ways. Pending a large-scale clinical trial or two to corroborate efficacy and safety, saffron may indeed have a role for weaning off maintenance opioid therapy in the not-too-distant future. ■

REFERENCE

1. Modabbernia A, Akhondzadeh S. Saffron, passionflower, valerian and sage for mental health. *Psychiatr Clin North Am* 2013;36:85-91.

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CME QUESTIONS

1. **Which of the following is true regarding dairy and Parkinson's disease (PD) risk?**
 - a. Consumption of all dairy was not associated with increased PD risk.
 - b. Consumption of low-fat dairy was associated with increased PD risk.
 - c. Consumption of high-fat dairy was associated with increased PD risk.
 - d. Men who consume dairy are more at risk than women for developing PD.
2. **Which of the following is most true regarding the management of fibromyalgia?**
 - a. Aerobic exercise is a recognized core treatment for fibromyalgia symptom management with benefits to many, but with barriers to implementation, some patients with fibromyalgia cannot engage in this treatment.
 - b. Tai chi may be as effective as aerobic exercise in management of fibromyalgia symptoms, but prospective studies have not yet been completed and only observational studies are available.
 - c. Tai chi, in a head-to-head prospective study vs. aerobic exercise, showed greater effect at week 24 with an attenuation of this effect by week 52. However, active intervention stopped at week 24.
 - d. Both a and c
3. **Mindfulness-based stress reduction is associated with which of the following?**
 - a. Decreases in ACTH and cortisol, but no change in IL-6 and TNF-alpha
 - b. Reductions in self-reported anxiety, but no blood marker changes
 - c. Increases in self-reported anxiety and increases in biomarker changes
 - d. Decreases in ACTH, cortisol, IL-6, and TNF-alpha
4. **Which of the following is true regarding the clinical use of saffron in the study by Nemat Shahi M, et al?**
 - a. It was dosed at 300 milligrams daily.
 - b. There was clear benefit in helping people wean off of maintenance oxycodone.
 - c. There was a trend of decreasing "temptation" in the saffron group over the eight-week study.
 - d. Both saffron and the control groups had increasing diarrhea over the course of the study period.

CME OBJECTIVES

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

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- 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.

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