AHC Media

Integrative Medicine

Vol. 17, Issue 6, June 2014
www.ahcmedia.com

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

STRESS AND ANXIETY

ABSTRACT & COMMENTARY

Meditation Effectiveness for Stress-related Outcomes

By Nancy Selfridge, MD

Associate Professor, Chair, Department of Clinical Medicine, and Assistant Dean, Clinical Sciences, Ross University School of Medicine, Commonwealth of Dominica, West Indies

Dr. Selfridge reports no financial relationships relevant to the field of study.

SYNOPSIS: A systematic review and meta-analysis of randomized controlled trials of meditation programs demonstrated moderate strength of evidence for mindfulness meditation for improving anxiety, depression, and pain.

SOURCE: Goyal M, et al. Meditation programs for psychological stress and well-being: A systematic review and meta-analysis. *JAMA Intern Med* 2014;174:357-368.

In order to assess the strength of evidence for recommending meditation programs as effective interventions for stress-related health problems, the authors conducted a systematic review and meta-analysis of randomized clinical trials of meditation compared to an active control group. Longitudinal studies of adult subjects with medical or psychiatric stress-related diagnoses and a structured protocol-based meditation program with at least 4 hours of training were additional inclusion criteria. Both mantra-based (e.g., transcendental meditation) and mindfulness-based (e.g., mindfulness-based stress reduction) programs were included. Trials had to include an active control group matched in time and attention to the intervention group. Forty-seven trials with 3515 participants resulted from this literature review process. Effects of meditation on several outcomes were evaluated: negative affect (anxiety, depression), positive affect (sense of well-being), health-related quality of life, attention, pain, weight, and stress-related behaviors impacting on health (substance use, sleep). Trials were evaluated for intervention fidelity, including quantity of structured training, home practice recommended, instructor qualifications, and descriptions or measures of participant adherence.

To display and compare outcome data from these trials, the authors calculated the relative difference in change scores, computed by taking the change

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Integrative Medicine
The Clinician's Evidence-Based Resource on Complementary Therapies [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (ISSN 1096-942X) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.

POSTMASTER: Send address changes to Integrative Medicine Alert, P.O. Box 550669, Atlanta, GA 30355.

Copyright © 2014 by AHC Media. 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.

Back Issues: Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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. The publication is not intended for use by the layman.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Questions & Comments:
Please contact Executive Editor **Leslie Coplin** at leslie.coplin@ahcmedia.com

Subscription Prices
United States
$319 per year.
Add $19.99 for shipping & handling.
$269 per year: Online only, single user

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Outside the United States
$369 per year plus GST.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of ***24 AMA PRA Category 1 Credits™***. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 24 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.

For CME credit, add $50.

AHC Media

from baseline in the treatment group, subtracting the change from baseline in the control group and dividing by the baseline score in the treatment group. This calculation allowed an estimate of the direction and magnitude of effect for all studies.

Control groups were classified as nonspecific active or specific active. Nonspecific active control groups — e.g., educational training — consisted of programs that matched the meditation intervention in terms of time and contact but did not represent a known intervention for the problem, allowing control for the nonspecific effects of time, attention, and participant expectations and more accurate measures of the efficacy of meditation. Specific active controls — e.g., drugs, exercise, and other behavioral therapies — allowed for comparisons of meditation with interventions known or expected to improve clinical outcomes.

Authors further assessed the included trials for strength of evidence using grading schemas and tools primarily from *Methods Guide for Conducting Comparative Effectiveness Reviews*, a publication of the Agency for Healthcare Research and Quality, supplemented with tools from the Cochrane Collaboration to assess risk of bias. Strength of evidence was stratified into four categories: high (high confidence that the evidence reflects the true effect; further studies are unlikely to change this confidence), moderate (moderate confidence that the evidence reflects the true effect; further studies may change this confidence), low (low confidence that the evidence reflects the true effect and further research is likely to change both confidence in the effect and the estimate of effect), and insufficient (evidence unavailable or inadequate for a conclusion).

Mindfulness meditation programs demonstrated moderate strength of evidence for improving anxiety (effect size 0.38 [95% CI, 0.12-0.64] at 8 weeks and 0.22 [95% CI, 0.02-0.43] at 3-6 months), depression (0.30 [95% CI, 0.00-0.59] at 8 weeks and 0.23 [95% CI, 0.05-0.42] at 3-6 months), and pain (0.33 [0.03-0.62]). Low strength of evidence was noted for improving stress/distress and mental health-related quality of life. Mantra-based meditation programs demonstrated low or no effect on multiple outcomes or insufficient evidence existed to make a judgment. Meditation programs appeared no better or worse than any active intervention in the specific active control trials. Though the meditation interventions were divided into mindfulness-based and mantra-based in the analysis, no sub-analyses were performed grouping types of active control interventions. The authors stated that there were no reported adverse effects in any of the trials chosen for review and analysis. They did not comment on any contraindications based on baseline mental health or risk of psychosis.

■ COMMENTARY

A previous summary of mindfulness research reported evidence that mindfulness training reduces negative emotion and perceived stress.[1] The body of research on meditation, however, includes observational studies, controlled trials using passive control strategies such as "wait-listing" that does not control for time, attention and expectation, and studies of inadequate sample size. The greatest value of this systematic review and analysis by Goyal et al is the inclusion of only randomized trials with active controls and their rigorous attempt to grade the strength of evidence in these selected trials, a process necessary to create the data needed to support clinical guidelines. Calculating and comparing standardized mean differences in effect sizes between studies with diverse outcome measures was an additional strength of this review.

Nonetheless, evaluating meditation research is fraught with challenges. Protocol interventions vary in format and duration. Trainer criteria, in terms of experience with meditation and/or teaching, are not specified or are not reported at all, though intuitively the experience and expertise of the teacher should have some impact on the student and outcomes. The authors cite four main biases in the relatively high-quality studies they chose for

Summary Points

- Mindfulness meditation interventions, though not mantra-based meditation interventions, demonstrate moderate strength of evidence for improving anxiety, depression, and pain.
- Mindfulness meditation appears no better or worse than other interventions known or expected to be effective for these problems, such as drugs, exercise, and other behavioral therapies.

review: lack of blinding of outcomes, lack of allocation concealment, lack of intention-to-treat analysis of data, and high attrition of participants. Though brain functional changes associated with positive affect have been reported after just 8 weeks of mindfulness-based stress reduction training consisting of approximately 27 hours of direct instruction, the effective dose of a meditation intervention for optimum treatment of stress-related health problems is unknown.[2] Several studies over the last decade studying brain changes in meditating monks suggest that neural effects of meditation noted on fMRI certainly increase with time and meditation experience. Most meditation trials are of very short duration. More time with expert training and dedication to practice might result in a level of skill and mastery that would demonstrate an even larger effect size on these studied outcomes than recent trials suggest. Rigorously constructed and implemented randomized, active, controlled trials of longer duration are necessary to resolve remaining questions and concerns about the efficacy and comparative effectiveness of meditation as an intervention.

More than 3 decades of research support mindfulness-based meditation as a health-promoting and potentially therapeutic intervention. This study graces us with an analysis of some of the best of this research for medical decision-making.

This review affirmed that no adverse effects of meditation were reported in any of these randomized, controlled trials. With this review and analysis as support, clinicians can confidently discuss with patients the potential effectiveness and safety of meditation as an intervention or adjunctive therapy for anxiety, depression, and pain, and state that it appears to work as well as other intervention programs shown or believed to be effective. Choosing between interventions will boil down to the personal preference of the patient as part of shared decision-making processes until further research suggests a clear advantage of meditation practices for these problems. ■

References

1. Greeson J. Mindfulness research update: 2008. *Complement Health Pract Rev* 2009;14:10-18.
2. Davidson RJ, et al. Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med* 2003;65:564-570.

CANCER, DIABETES, OBESITY

ABSTRACT & COMMENTARY

Metabolic Dysregulation and the Risk of Obesity-related Cancers

By Traci Pantuso ND, MS

Adjunct Faculty, Bastyr University, Seattle, WA

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

SYNOPSIS: This study investigates the role of metabolic dysregulation of the insulin-glucose axis and the risk of obesity-related cancers in the Framingham Heart Study Offspring Cohort over approximately 37 years. The authors found that impaired fasting glucose exposure for a period greater than 10 years increased obesity-related cancer risk.

SOURCE: Parekh N, et al. Metabolic dysregulation of the insulin-glucose axis and risk of obesity-related cancers in the Framingham heart study-offspring cohort (1971-2008). *Cancer Epidemiol Biomarkers Prev* 2013;22:1825-1836.

Thirty-five percent of adults meet the clinical criteria for obesity in the United States, which is considered a nationwide health epidemic. Excess adiposity is a well-established risk factor for several cancers, according to the World Cancer Research Fund/American Institute for Cancer Research Expert Panel Report.[1] Excess adiposity is also an established risk factor for type 2 diabetes mellitus (T2DM). Recently, multiple meta-analyses have demonstrated that T2DM is an independent risk factor for particular types of cancer.[2]

Summary Points

- Individuals with impaired fasting glucose (IFG) had a 27% higher risk of developing obesity-related cancers compared to those who did not have IFG.
- A 44% increased risk of obesity-related cancer in participants who had IFG detected 10-20 years prior was observed. This risk increased to 57% for participants who had IFG detected > 20 years prior.
- A risk estimate for colorectal cancer > 3 was observed in participants who were exposed to IFG for more than 20 years.

Excess adiposity is known to secrete cytokines and other products that cause chronic inflammation and are thought to influence neoplastic processes.[2] Biomarkers for insulin resistance and elevated blood glucose may indicate metabolic processes that increase cancer risk. The authors of this study investigated the relationship between a number of different clinical and laboratory metabolic biomarkers with the development of obesity-related cancers as an endpoint.

Methods. The study population for this study was the Framingham Offspring Cohort from the Framingham Health Study (FHS). The FHS is a three-generational study that is taking place in Framingham, Mass. The study population was > 20 years old and had no diagnosis of type 1 diabetes or cancer at onset of study. Clinic exams occurred on average every 4 years from 1971-2008. Data on women who were pregnant at the time of an exam were not included, as they would falsely elevate a number of the biomarkers for that exam.

The authors investigated a number of biomarkers to evaluate the insulin-glucose axis. Fasting blood glucose was measured at every exam while hemoglobin A1c and fasting insulin concentration were measured at select exams. The authors used blood glucose and insulin concentrations at exams 5 and 7 to calculate the homeostatic model assessment-insulin resistance (HOMA-IR). HOMA-IR measures pancreatic ß-cell function and insulin resistance. Blood pressure, height, and weight were measured at every exam visit. Waist circumference was measured at five of the eight exams. Physical activity was self-reported and a physical activity index (PAI) was calculated. The Harvard food frequency questionnaire was used to evaluate diet during exams 5 through 8. Other information that was collected during visits was occupation, education, ethnicity, multivitamin use, alcohol, smoking, medication, and medical history.

The authors evaluated the primary outcome of obesity-related cancers, which includes cancers of the thyroid gland, genitourinary organs, female reproductive tract, reticuloendothelial system (blood, bone, and spleen), and the gastrointestinal tract. Skin cancers were excluded from this analysis. The majority of cancers were confirmed primary cancers from pathology reports with the date of diagnosis. Less than 5% of cancers were confirmed by either death certificates or clinical reports without pathology reports. The authors used the Cox proportional hazards model with time dependent covariates to evaluate the risk of obesity-related cancer using all available data.

Results. There were a total of 4615 participants; 99% were Caucasian and 50% were female. The mean age at baseline was 37.5 years and 66.8 years at the last exam. Both body mass index (BMI) and waist circumference increased over time (*see Table 1*). There was no evidence of energy intake variability during the dietary follow-up period, and the physical activity index scores measured a moderate activity level with a range of scores from 34.6 to 37.7 units.

Primary Outcome. There were 787 confirmed obesity-related cancers identified: 136 colorectal cancers, 219 prostate cancers, and 217 breast cancer.

Participants who had IFG detected 10-20 years and 20 + years had an increased risk (44% and

Table 1. BMI and Waist Circumference at Baseline and Endpoint

	Baseline	Endpoint	*P* value
BMI (kg/m^2)	25.6	28.3	$P < 0.0001$
Female waist circumference (inches)	32.4	38.9	$P < 0.0001$
Male waist circumference (inches)	38.5	41.4	$P < 0.0001$

Table 2. Risk of Obesity-Related Cancers and IFG Exposure Time

Time from IFG	Risk %	Adjusted HR	
5-10 years		1.13 (0.91-1.41)	Not significant
10-20 years	44%	1.44 (1.15-1.79)	
20+ years	57%	1.57 (1.17-2.11)	
P_{trend}		0.1477	

57%, respectively) of obesity-related cancers when adjusted for age and other covariates (*see Table 2*). There was no significance found for impaired fasting glucose (IFG) exposure 5-10 years prior to a cancer diagnosis even though the hazard ratio (HR) was > 1 (*see Table 2*).

Compared to individuals without IFG, there was a 27% higher risk of developing obesity-related cancer among participants with IFG (HR, 1.27; 95% confidence interval [CI], 1.06-1.53) after adjusting for age, sex, alcohol, smoking, and BMI.

Homeostatic model assessment-insulin resistance (HOMA-IR), first reported in 1985, assesses insulin sensitivity and ß-cell function. A 45% increase in risk of obesity-related cancers was noted with a HOMA-IR score of > 2.6 (HR, 1.45; CI, 1.18-1.78).

There was a 54% increased risk of developing obesity-related cancers among persons within the highest vs the lowest category of HbA1c levels (CI, 1.13-2.1). A 47% increased risk of obesity-related cancers among participants within the highest (≥ 9.94 pmol/L) compared to the lowest (< 4.94 pmol/L) group of blood insulin concentrations was also found (CI, 1.15-1.88).

Many participants quit smoking, which was indicated by the increase in the number of past smokers over time (20.2-51.3%; $P < 0.0001$). There was an increased risk of obesity-related cancers among past or current smokers who also had higher glucose concentrations (HR, 1.41; CI, 1.13-1.76).

Specific Obesity-Related Cancers. There was a significant increased risk for developing colorectal cancer with the increased IFG exposure time (P_{trend} = 0.0196). Participants who were exposed to IFG for more than 20 years had a risk estimate over 3. No significant association between IFG exposure time and risk of breast or prostate cancer were found.

An increased risk of colon cancer that was more than two-fold was found when participants had higher concentrations of the glucose metabolism biomarkers but not higher waist circumference. The authors also point out that there was a trend of increased risk of breast cancer with all of the glucose metabolism biomarkers, with HRs ranging from 1.23-1.95, but not with waist circumference. A nonsignificant HR for developing prostate cancer that ranged from 1.10-1.52 was also reported.

■ COMMENTARY

This study has demonstrated that IFG time exposure increases the risk of obesity-related cancers, particularly colorectal cancer. This study is unique in that the researchers were able to also investigate the time variable in relation to IFG and the association to obesity-related cancers. This research study had a number of strengths and a few weaknesses. The strengths of this study are the large participant group, of which 50% were female, and a 37-year follow-up period with exams occurring approximately every 4 years. The diagnosis of cancer was provided by the participant's doctor and confirmed with the pathology reports in most cases. There were also dietary, medication, anthropometric, physical activity, and demographic data that allowed the researchers to control for variables that are known risk factors of cancer.

The limitations of this study include the lack of generalizability to other ethnicities, as the population was 99% Caucasian. Also, family medical history of cancer was not available and is a known risk factor. Another issue with this study that the authors point out is with the risk of prostate cancer in men with IFG. The authors mention that they believe the lack of an association between IFG and the risk of prostate cancer may be underestimated due to decreased rate of diagnosis in this population. The authors make the argument that prostate-specific antigen concentrations may be decreased in men who are obese and have glucose abnormalities leading to a lack of follow-up prostate biopsies.

Obesity has reached epidemic proportions in the United States.[2,4] Recently, the American Medical Association categorized obesity as a disease and with this recognition it is believed it will be treated as a disease. Obesity is a multifactorial disease that must be addressed on a number of levels including

the mental, emotional, and physical health of an individual. The best treatment for obesity is through diet and lifestyle modifications, which are preventive measures. This study demonstrates the important connections between IFG and obesity-related cancers. More research needs to be performed to understand the best way to recommend and follow up with diet and lifestyle recommendations so that patients are able to implement them successfully and reduce obesity and fasting glucose levels. ■

References

1. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: A global perspective. Washington, DC: AICR; 2007.
2. Garg SK, et al. Diabetes and cancer: Two diseases with obesity as a common risk factor. *Diabetes Obes Metab* 2014;16:97-110.
3. World Health Organization/IDF Consultation. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia. Geneva; 2006.
4. Haslam DW, James WP. Obesity. *Lancet* 2005;366:1197-1209.

DIETARY SUPPLEMENTS

ABSTRACT & COMMENTARY

The Drawbacks of Retrospective Dietary Supplement Monitoring

By David Kiefer, MD

SYNOPSIS: This study reviews a recent example of hepatotoxicity from a dietary supplement and discusses the issues related to retroactively monitoring nutritional supplements for adverse effects.

SOURCE: Cohen PA. Hazards of hindsight — Monitoring the safety of nutritional supplements. *N Engl J Med* 2014;370:1277-1280.

This article tracks the chronology of adverse effects to OxyElite Pro, a dietary supplement containing caffeine and four herbal ingredients (*Bauhinia purpurea*, *Bacopa monnieri*, *Cirsium oligophyllum*, and yohimbe, *Pausinystalia johimbe*), that was marketed to help people "burn fat." The product, which has since been recalled, was first noted to cause hepatitis and, sometimes, liver failure in May 2013, but it took the FDA 4 months to learn of the problem and start an investigation. All told, 97 cases were linked to OxyElite Pro, including 47 hospitalizations, three liver transplantations, and one fatality.

The author accurately reviews the ultimate origin of the reporting delay in this case example. Due to 1994 legislation (the Dietary Supplement Health and Education Act, abbreviated DSHEA and often pronounced "deh shay"), the 85,000 dietary supplement products in the United States can be released for sale to the public without the phases of proof of safety or efficacy that are required for pharmaceuticals. All monitoring for dietary supplements takes place retroactively, and the FDA relies on MedWatch, a voluntary reporting system. Of note, attempts to change this arrangement repeatedly have failed due to outcry from industry and the public, due, in part to the desire to have unfettered access to vitamins and herbs in the over-the-counter or online environments, where most of these products are sold.

This article is not a clinical trial nor meta-analysis, but rather a commentary type review, and it mentions concerns about adulteration. For example, over an undisclosed time period, 500 supplements have been found to be adulterated, including two with "new" stimulants that were found in 2013. The author also mentions one stimulant adulterant that was identified in the author's laboratory. In addition, the article provides a table of potential adverse reactions to "legal ingredients and adulterants in dietary supplements" (*see abbreviated Table*), although no sources were given for the information provided. Twice, NSAIDs were listed, though it was unclear if those are known adulterants or "legal ingredients" in dietary supplements.

Mention is made of the confusion surrounding this topic on the part of clinicians or the concerned public, how reports are sometimes made to local poison control centers, and how investigations may begin with other governmental groups such as public health departments, the Department of Defense, or the Centers for Disease Control and Prevention. With so many people and organizations involved, the author posits that it is easy to understand why a delay might occur in the reporting of an adverse dietary supplement effect.

The Dietary Supplement Labeling Act, pending in Congress, may lead to some improvement through required product registration with the FDA and lists of known adverse effects. Other suggestions

Summary Points

- Dietary supplement monitoring takes place retroactively and involves several different groups, which can delay the removal of unsafe supplements from store shelves.
- A recent example of this is well-documented hepatotoxicity from OxyElite Pro, a supplement marketed to help burn fat.
- Some solutions to the problems associated with retroactive surveillance are new labeling legislation, database sharing, and an advisory team of experts.

for going forward include the sharing of databases between the groups mentioned above; a central clearinghouse where all of that data are combined, stored, and accessible; and a team of experts to assist health care providers with their supplement questions and concerns.

The author's parting comments make clear the main point of the article: "But even these ambitious changes would not prevent dangerous supplements from reaching consumers. If consumers and physicians are to have confidence that all supplements are safe, the law regulating supplements must be reformed. Every supplement ingredient should undergo rigorous safety testing before marketing."

■ COMMENTARY

This article received media coverage and seems to nudge (push?) the consumer and health care providers toward feeling like it is dangerous to drink bottled herbal tea, take vitamin C, or ingest any of the 85,000 dietary supplements available in the marketplace; the current climate of retrospective dietary supplement monitoring is dangerous, replete with adverse effects and pharmaceutical interactions, so beware! A more balanced view of this topic would agree with some, but not all, of the author's points.

For example, there is no doubt that there are some unsafe products for sale, but in context, many botanical medicines have years of safe and effective traditional use, some mounting clinical evidence, Good Manufacturing Practice (GMP) oversight that is now legally mandated, and third-party certification efforts (such as ConsumerLab and the United States Pharmacopeia) that are addressing the issue of safety. One could argue that some of the energy of safety vigilance should be turned to a greater public health concern — the morbidity, mortality, and polypharmacy associated with pharmaceutical use, not an insignificant concern.[1,2,3]

Perhaps the author's recent discovery of an adulterant in a popular sports supplement scared him. And, it seems, for good reason; he reports finding an analog of methamphetamine that has never been used nor studied in humans, potentially a serious, if not dangerous, situation. Such products are unacceptable and should never be found on the store shelves. His suggested improvements via labeling legislation, database sharing, and a team of experts whose sole purpose is to guide confused clinicians faced with a possible adverse effect all seem like good ideas and worth government funding. And, the author is right about the inadequacies of the MedWatch system to thoroughly characterize possible adverse dietary supplement effects. Product

Table. Summary of Potential Adverse Dietary Supplement Reactions Noted by Author

The following information appears in the table in the article reviewed. The information is both potentially accurate but also misleading.

Symptoms	Ingredients possibly responsible
Arrhythmias	*Ephedra* spp, *Epimedium* spp (Horny goat weed)
Bleeding	Ginkgo biloba, NSAIDs
Gynecomastia, acne, hirsutism, infertility	DHEA
Hepatotoxicity	*Symphytum officinale* (comfrey), *Piper methysticum* (kava kava), *Larrea tridentata* (chaparral)
Mood alterations	*Panax ginseng*
Nausea, vomiting, diarrhea, anorexia	*Crataegus* spp (hawthorn)
Nephrolithiasis	Calcium
Rash	*Hypericum perforatum*

Adapted from: Cohen PA. Hazards of hindsight — Monitoring the safety of nutritional supplements. *N Engl J Med* 2014;370:1277-1280.

name, lot numbers, chronology, and dose are some key pieces of information required to pin an effect on a given substance, and to leave that detective work up to busy clinicians volunteering their time to access an online report form is a recipe for incomplete reporting. The proposed legislation may function to improve this situation, but it begs the question of how registering safety information with the FDA will occur when many products have little to no data, and there is little to no incentive, if it isn't mandated, to do the expensive studies necessary to determine safety. Partnerships between researchers, industry, and government seem crucial to providing information necessary to making all of these decisions.

It is all too easy to fan the negative media fire about dietary supplements, but more useful to clinicians is a discussion grounded in scientific articles and high-quality references. The misinformation in the Table provided by the author is anything but scientific: lacking references, correct botanical nomenclature, or relevance to the topic of adverse effect reporting. For example, arrhythmias, myocardial infarction, and stroke are listed as being caused by ephedra, true, but ephedra (*Ephedra sinica*) and ephedrine alkaloids have been banned since the early 2000s due to their adverse cardiovascular effects; the inclusion of "illegal" substances in a table labeled as "legal" seems unnecessary and misleading, perhaps representing the author's bias. The inclusion of NSAIDs seems equally irrelevant and not very useful to clinicians trying to learn about the topic. Also, well-known adverse effects, such as a few possible case reports of bleeding from *Ginkgo biloba* or the photo-induced rash from *Hypericum perforatum*, and adverse gastrointestinal effects from numerous dietary supplements, are no surprise, and don't really seem relevant to the topic of surveillance. These latter adverse effects and those of other dietary supplements seem better addressed through improved patient and provider education and increased rates of disclosure of use.[4,5,6] Again, to include such a table here seems to unnecessarily feed hysteria.

In summary, it is extremely important that safe, high-quality dietary supplements, free of adulteration, be available for use in the United States, and that all clinicians get in the habit of checking for adverse effects or supplement-pharmaceutical interactions for each patient. This article makes some useful suggestions about improving surveillance and marketing of dietary supplements in the United States at the same time that some of the data provided are misleading, out of useful context, and distracting, a reminder of the importance of an evidence-based discourse about dietary supplements and other integrative therapeutics. ■

References

1. Miguel A, et al. Frequency of adverse drug reactions in hospitalized patients: A systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf* 2012;21:1139-1154.
2. Lazarou J, et al. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *JAMA* 1998;279:1200-1205.
3. Nisly NL, et al. Dietary supplement polypharmacy: An unrecognized public health problem. *Evid Based Complement Alternat Med* 2010;7:107-113.
4. Kiefer D, et al. The overlap of dietary supplement and pharmaceutical use in the MIDUS National Study. *Evid Based Comp Alternat Med* April 2014. Article ID 823853. http://dx.doi.org/10.1155/2014/823853.
5. Gardiner P, et al. Factors associated with herbal therapy use by adults in the United States. *Altern Ther Health Med* 2007;13:22-29.
6. Barnes PM, et al. Complementary and alternative medicine use among adults and children: United States, 2007. *National Health Statistics Report* 2009;12:1-23.

ANXIETY

Some Dietary Supplements for Anxiety

By Todd A. Born, ND

Born Naturopathic Associates, Inc., Alameda, CA; Product Manager, Allergy Research Group LLC

Dr. Born reports that he is a consultant for Nutri-Link Clinical Education.

These are stressful times, or at least there are times when many patients feel ill-equipped to manage their stressors — whether it is the economy, jobs, inclement weather, their own health or the health of loved ones, or even the health of pets. Over time, these events may take deleterious tolls. For example, numerous studies link anxiety and stress with cardiovascular disease. Not only do anxiety and stress increase disease incidence, but they also increase the risk of an adverse cardiovascular event (stroke or heart attack). Studies have shown that the prevalence of anxiety is high (approximately 70-80%) among patients who have experienced an acute cardiac event.[1] Even among the patients who have not experienced these events, the prevalence of anxiety is estimated to be between 20-25%.[1]

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) discusses the various conditions within the anxiety spectrum; a full review of the

Summary Points

- Anxiety disorders affect more than 40 million U.S. adults.
- Patients with anxiety disorders who do not tolerate pharmaceutical medications may consider nutritional and/or herbal interventions.
- Nutritional/herbal interventions have the potential to interact with psychoactive pharmaceuticals, so concomitant use should be avoided.

diagnosis of these conditions, however, is beyond the scope of this article. Along this spectrum are panic attacks, phobias, obsessive-compulsive disorder, post-traumatic stress disorder, and generalized anxiety and its subsets. Anxiety is even more prevalent than depression, and many times these two diagnoses go hand in hand.[2] Prior to any intervention, it is important to rule out organic causes such as hyperthyroidism, carcinoid syndrome, pheochromocytoma, and numerous others. Anxiety can be acute (2 days to 4 weeks) or chronic (occurs more days than not for at least 6 months). In the short term, moderate amounts of anxiety can be a beneficial part of our existence, such as alerting us to danger or perhaps even increasing our performance. But chronic or severe anxiety can take over one's life and interrupt daily activities, interrupt sleep, lead to poor dietary choices, and make one exercise less, and even to the point one just doesn't even want to go out and socialize. This can lead to serious health concerns and cause or amplify relationship issues.[3,4]

PATHOPHYSIOLOGY

Genetic factors appear to predispose individuals to the development of generalized anxiety disorder (GAD). Data from twin studies have been inconsistent, but what has been seen is in the serotonin transporter gene-linked polymorphic region SS genotype (short/short). This gene has been found to be more frequent in patients with GAD.[6] Another theory is the variations in two subtypes of the glutamic acid decarboxylase gene, which may increase individual susceptibility to anxiety disorders, including GAD.[7]

On the topic of genetics, methylenetetrahydrofolate reductase (MTHFR) polymorphisms have clear links to mood, anxiety, and personality disorders. The MTHFR gene provides instructions for making the enzyme methylenetetrahydrofolate reductase, which plays a role in processing amino acids. MTHFR is important for a chemical reaction involving forms of the B vitamin folate (folic acid or vitamin B9). Specifically, this enzyme converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.[8,9]

Neuroimaging and other studies suggest the symptoms of GAD are accompanied by an enhanced emotional responsiveness in fear-related brain circuits. A 2009 study using functional MRI (fMRI) showed that patients who had GAD showed greater anticipatory activity than healthy controls in the bilateral dorsal amygdala.[10]

Higher-than-average number of traumatic experiences and other undesirable life events in childhood have been found to increase prevalence of GAD.[11] GAD is more likely to occur in people with behavioral inhibition — a tendency to be timid and shy in new situations.[12]

Anxiety is multifactorial and can stem from a myriad of causes or a combination of them. Besides the aforementioned pathological conditions, caffeine, poor sleep habits, poor diet, unique nutrient deficiencies, lack of exercise, and other reasons can all play a factor.[13,14]

ALLOPATHIC APPROACH

Conventionally, anxiety, regardless of etiology or form, tends to be managed primarily with antianxiety medications, antidepressants, sleeping medications, and at times, counseling, cognitive behavioral therapy, or more recently mindfulness.[15] With respect to the latter, there is increasing evidence of efficacy of mindfulness-based stress reduction and other behavioral health and mind-body techniques in

Anxiety Facts[5]

- Anxiety disorders are the most common mental illness in the United States, affecting 40 million U.S. adults age 18 and older (18% of U.S. population).
- Anxiety disorders cost the United States more than $42 billion a year, almost one-third of the country's $148 billion total mental health bill.
- More than $22.84 billion of those costs are associated with the repeated use of health care services; people with anxiety disorders seek relief for symptoms that mimic physical illnesses.
- People with an anxiety disorder are three to five times more likely to go to the doctor and six times more likely to be hospitalized for psychiatric disorders than those who do not suffer from anxiety disorders.
- Anxiety disorders develop from a complex set of risk factors, including genetics, brain chemistry, personality, and life events.

anxiety (see article on page 61).

More patients seem to be looking into safer "alternatives" to medications. Natural does not necessarily equate to safe, but evidence-based nutraceutical interventions for anxiety disorders are available. Patients who do not tolerate the current medications may consider nutritional and herbal interventions. It can be difficult to define what is integrative medicine and what is conventional or allopathic medicine, especially as once-unconventional therapies become more and more accepted (i.e., mindfulness-based stress reduction). That said, some therapies may not be considered mainstream and still have some evidence of efficacy as adjunctive treatments, or outright substitutions for the treatments, such as pharmaceuticals, that may have significant adverse effects. Some examples of such therapies, and their dosing and important references, are listed below. Clinicians must assess their patients and decide what they believe may be most effective for each individual.

Withania somnifera (ashwagandha) is an Ayurvedic (East Indian) that has antiaging, hematopoietic, immunomodulating, anxiolytic, antidepressant, cardiovascular protection, antitumor and antineoplastic properties. Dosage is 3000-6000 mg of dried root or 300-500 mg standardized extract.[16,17,18] A 2012 study of 64 volunteers randomized subjects to either ashwagandha or a placebo twice a day for 60 days. On day 60, significant reduction in stress scores and substantial reduction in cortisol levels were observed compared to placebo.[16]

L-theanine (200-400 mg daily) is an amino acid found in tea (higher amounts in green tea) that can reduce anxiety.[19,20] L-theanine can increase levels of gamma-aminobutyric acid (GABA) and serotonin. In 2011, an 8-week randomized, double-blind, two-center, placebo-controlled trial sought to see if L-theanine would be effective at relieving positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder. The authors found that L-theanine was a safe and well-tolerated augmentation of antipsychotic therapy, which can "ameliorate positive, activation, and anxiety symptoms in schizophrenia and schizoaffective disorder patients."

GABA (100-200 mg up to three times daily) has natural relaxant effects.[21] A 2006 study used EEG-measured alpha waves on 13 subjects given either water, L-theanine, or GABA. After 60 minutes of administration, GABA significantly increased alpha waves and decreased beta waves compared to water or L-theanine.[22] In the second part of the study, eight acrophobic subjects received either GABA or placebo. All subjects crossed a suspended bridge. Immunoglobulin A (IgA) saliva levels were monitored during bridge crossing. The placebo group showed a marked decrease in their IgA levels, while the GABA group showed significantly higher levels.[22]

Inositol (12-18 g per day) was found to be equivalent or better than fluvoxamine.[23,24] In a double-blind, randomized, controlled trial (RCT), Palatnik et al found that the number of panic attacks in the inositol group reduced by an average of four episodes compared to 2.4 from fluvoxamine over a 1-month period. Nausea and tiredness were more common with fluvoxamine, whereas inositol was well tolerated.[23]

Omega-3 essential fatty acids reduce inflammation and anxiety at 2500 mg daily.[25] In a 12-week, double-blind RCT, 68 medical students had blood drawn at baseline and under stressful conditions (before an exam). Lipopolysaccharide (LPS), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6) were measured. The subjects were given either 2085 mg EPA/348 mg DHA or placebo. LPS and TNF-α decreased, IL-6 increased, while secondary analyses that used the plasma n-6:n-3 ratio in the treatment group showed that decreasing n-6:n-3 ratios led to lower anxiety. The authors concluded, "The reduction in anxiety symptoms associated with n-3 supplementation provides the first evidence that n-3 may have potential anxiolytic benefits for individuals without an anxiety disorder diagnosis."

Piper methisticum (kava kava) can be given 150-400 mg in divided doses of standardized extract (70% kavalactones).[26,27] A 2003, 8-week, double-blind RCT involving 129 patients showed that kava kava LI150 is well tolerated and is as effective as buspirone and opipramol in the acute treatment of outpatients with GAD.[26] Due to concerns about hepatotoxicity, most experts recommend monitoring liver enzymes at baseline and every 6 months if using kava kava long term. It should be avoided in people with preexisting liver disease.

Passiflora incarnata (passion flower) at 45 drops per day of a tincture (1:8 in 45% alcohol) was found to be just as effective as oxazepam.[28] A double-blind RCT involving 36 outpatients found passion flower extract to be equivalent to oxazepam in GAD. The passion flower was well tolerated, while the participants who took oxacepam experienced significantly more problems relating to impairment of job performance.[28]

Silexan is a lavender oil capsule (80 mg daily) used

as an alternative to benzodiazepines.[29] A 2010 multicenter, double-blind RCT looked into the efficacy of a 6-week intake of silexan vs lorazepam. The primary target variable was the change in the Hamilton Anxiety Rating Scale (HAM-A). The mean of the HAM-A-total score decreased clearly and to a similar extent in both groups. Silexan showed no sedative effects, has no potential for drug abuse, and, therefore, may be considered an alternative to benzodiazepines for GAD.

Rhodiola rosea (100-400 mg daily), known for its adaptogenic properties, decreases anxiety and enables better adaptation to stress response.[30,31] Use with caution in patients with bipolar disorder.

ADVERSE EFFECTS AND INTERACTIONS WITH ALLOPATHIC THERAPEUTICS

All of the aforementioned interventions have the potential to interact with psychoactive pharmaceuticals, including additive effects with anxiolytics, so concomitant use should be avoided or done cautiously. In addition, GABA and L-theanine may theoretically potentiate antihypertensives, so caution is advised.[32,33]

Precautions should be taken with certain conventional treatments, including selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors, which block reabsorption (reuptake) of the neurotransmitter serotonin in the brain and block the absorption (reuptake) of the neurotransmitters serotonin and norepinephrine in the brain, respectively.[34,35] Nutrients like tryptophan, 5-hydroxytryptophan, and s-adenosylmethionine can increase the amount of serotonin, and combined with the medication may cause serotonin syndrome (SS) in susceptible people. SS can range in severity from mild to life-threatening. Most cases of SS are mild and resolve with prompt recognition and supportive care.[36,37,38]

CONCLUSION

It has been observed that the greatest success at anxiety resolution is with a combination of the "recommendations," along with counseling and stress reduction techniques. The brilliance of integrative medicine is to take the patient's whole picture into account and determine an individualized treatment plan and strategy based upon the evidence-based treatment recommendations. ■

References

1. Nainggolan L. Anxiety Predicts Heart Disease Years Later. The Heart.org. June 2010. Available at: http://www.medscape.com/viewarticle/723944. Accessed May 14, 2014.
2. Stein MB, et al. *Anxiety Disorders. Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision. 4th ed. Washington DC: American Psychiatric Association; 2000: 429-84.
3. Anxiety. Mayo Clinic. Available at: http://www.mayoclinic.org/diseases-conditions/anxiety/basics/definition/con-20026282. Accessed May 15, 2014.
4. Moser DK. The rust of life: Impact of anxiety on cardiac patients. *Am J Crit Care* 2007;16:361-369.
5. Anxiety and Depression Association of America. Facts & Statistics. Available at: http://www.adaa.org/about-adaa/press-room/facts-statistics. Accessed March 7, 2014.
6. You JS, et al. Serotonin transporter and tryptophan hydroxylase gene polymorphisms in Chinese patients with generalized anxiety disorder. *Psychiatr Genet* 2005;15:7-11.
7. Donner J, et al. Support for involvement of glutamate decarboxylase 1 and neuropeptide Y in anxiety susceptibility. *Am J Med Genet B Neuropsychiatr Genet* 2012;159B:316-327.
8. National Institutes of Health. MTHFR. Genetics Home Reference. Available at: http://ghr.nlm.nih.gov/gene/MTHFR . Accessed May 14, 2014.
9. Gilbody S, et al. Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: A HuGE review. *Am J Epidemiol* 2007;165:1-13.
10. Nitschke JB, et al. Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. *Am J Psychiatry* 2009;166:302-310.
11. Safren SA, et al. History of childhood abuse in panic disorder, social phobia, and generalized anxiety disorder. *J Nerv Ment Dis* 2002;190:453-456.
12. Rosenbaum JF, et al. Behavioral inhibition in childhood: A risk factor for anxiety disorders. *Harv Rev Psychiatry* 1993;1:2-16.
13. Greden GJ. Anxiety or caffeinism: A diagnostic dilemma. *Am J Psychiatry* 1974;131:1089-1092
14. Uhde TW, et al. Caffeine: Relationship to human anxiety, plasma MHPG, and cortisol. *Psychopharmacol Bull* 1984;20:426-430.
15. Mayo Clinic. Anxiety, Treatments and Drugs. Available at: http://www.mayoclinic.org/diseases-conditions/anxiety/basics/treatment/con-20026282. Accessed May 14, 2014.
16. Chandrasekhar K, et al. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. *Indian J Psychol Med* 2012;34:255-262.
17. Withania somnifera. Alt Med Review Available at: http://www.thorne.com/altmedrev/.fulltext/9/2/211.pdf. Accessed May 15, 2014.
18. Winters M. Ancient medicine, modern use: *Withania somnifera* and its potential role in integrative oncology. *Altern Med Rev* 2006;11:269-277.
19. Ritsner MS, et al. L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: An 8-week, randomized, double-blind, placebo-controlled, 2-center Study. *J Clin Psychiatry* 2011;72:34-42.
20. Kimura K, et al. L-Theanine reduces psychological and physiological stress responses. *Biol Psychol* 2007;74:39-45.
21. Gamma-Aminobutyric Acid (GABA). *Alt Med Review* 2007:12:274-279.
22. Abdou AM, et al. Relaxation and immunity enhancement effects of gamma-aminobutyric acid (GABA) administration in humans." *Biofactors* 2006;26:201-208.
23. Palatnik A, et al. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *J Clin Psychopharmacol* 2001;21:335-339.
24. Benjamin J, et al. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. *Am J Psychiatry* 1995;152:1084-1086.
25. Kiecolt-Glaser JK, et al. Omega-3 supplementation lowers inflammation and anxiety in medical students: A randomized controlled trial. *Brain Behav Immun* 2011;25:1725-1734.
26. Boerner RJ, et al. Kava-Kava extract LI 150 is as effective as opipramol and buspirone in generalised anxiety disorder—an 8-week randomised, double-blind multi-centre clinical trial in 129

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

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

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

Mary Jo Kreitzer, PhD, RN
Director
Center for Spirituality and Healing
University of Minnesota
Minneapolis

Dónal O'Mathúna, BS (Pharm), MA, PhD
Senior Lecturer
Ethics, Decision-Making & Evidence
School of Nursing
Dublin City University, 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, WI

J. Adam Rindfleisch, MD, MPhil
Associate Professor, Associate Residency Program Director, Integrative Medicine Fellowship Director
Department of Family Medicine
University of Wisconsin, Madison

Howell Sasser, PhD
Associate, Performance Measurement Clinical Policy
American College of Physicians
Philadelphia, PA

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

EXECUTIVE EDITOR
Leslie Coplin

MANAGING EDITOR
Neill Kimball

EDITORIAL DIRECTOR
Lee Landenberger

out-patients. *Phytomedicine* 2003;10:38-49.
27. Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: Systematic review and meta-analysis. *J Clin Psychopharmacol* 2000;20:84-89.
28. Akhondzadeh S, et al. Passionflower in the treatment of generalized anxiety: A pilot double-blind randomized controlled trial with oxazepam. *J Clin Pharm Ther* 2001;26:363-367.
29. Woelk H, Schlafke S. A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. *Phytomedicine* 2010;17:94-99.
30. Spasov AA, et al. [The effect of the preparation rhodakson on the psychophysiological and physical adaptation of students to an academic load.] *Eksp Klin Farmakol* 2000;63:76-78.
31. Bystritsky A. A pilot study of *Rhodiola rosea* (Rhodax) for generalized anxiety disorder (GAD). *J Altern Complement Med* 2008;14:175-180.
32. Inoue K, et al. Blood-pressure-lowering effect of a novel fermented milk containing gamma-aminobutyric acid (GABA) in mild hypertensives. *Eur J Clin Nutr* 2003;57:490-495.
33. Yokogoshi H, Kobayashi M. Hypotensive effect of gamma-glutamylethylamide in spontaneously hypertensive rats. *Life Sci* 1998;62:1065-1068.
34. Depression. Selective serotonin reuptake inhibitors (SSRIs). Mayo Clinic Available at: http://www.mayoclinic.org/diseases-conditions/depression/in-depth/ssris/art-20044825. Accessed May 14, 2012.
35. Depression. Serotonin and norepinephrine reuptake inhibitors (SNRIs). Mayo Clinic Available at: www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20044970 Accessed May 14, 2012.
36. Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991;148:705-713.
37. Goff DC. Two cases of hypomania following the addition of L-tryptophan to a monoamine oxidase inhibitor. *Am J Psychiatry* 1985;142:1487-1488.
38. Bodner RA, et al. Serotonin syndrome. *Neurology* 1995;45:219-223.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.

2. Scan the QR code to the right, or log on to www.cmecity.com to take a post-test.

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. In a recent meta-analysis of randomized controlled trials, mindfulness meditation has demonstrated moderate strength of evidence for improving which of the following conditions?
a. Well-being
b. Anxiety
c. Attention
d. Sleep

2. What biomarkers indicate an increased risk for obesity-related cancers?
a. Waist circumference, HOMA-IR, HgbA1c, fasting insulin concentration
b. HgbA1c, waist circumference, fasting blood glucose
c. Fasting blood glucose, HgbA1c, waist circumference
d. HOMA-IR, fasting blood glucose, HgbA1c, fasting insulin concentration

3. Which of the following is true regarding the monitoring and investigation of adverse dietary supplement effects?
a. Sometimes the Centers for Disease Control and Prevention gets involved.
b. It is *prospective* in that dietary supplement companies have to submit extensive safety and efficacy studies prior to a product's release.
c. Adulteration of dietary supplements is not a problem in the United States.
d. The Dietary Supplement Labeling Act of 1994 governs all aspects of dietary supplement safety and efficacy.

4. Omega-3 essential fatty acids are dosed at 1000 mg daily to treat anxiety.
a. True
b. False

[IN FUTURE ISSUES]

Energy medicine concepts and interventions

Update on probiotics

Fish oil and cardiovascular disease

To reproduce any part of this newsletter for promotional purposes, please contact:
Stephen Vance
Phone: (800) 688-2421, ext. 5511
Email: stephen.vance@ahcmedia.com

For pricing on group discounts, multiple copies, site-licenses, or electronic distribution please contact:
Tria Kreutzer
Phone: (800) 688-2421, ext. 5482
Email: tria.kreutzer@ahcmedia.com

To reproduce any part of AHC newsletters for educational purposes, please contact:
The Copyright Clearance Center for permission
Email: info@copyright.com
Phone: (978) 750-8400