

# Complementary/Integrative Therapies That Work: A Review of the Evidence

BENJAMIN KLIGLER, MD, MPH, and RAYMOND TEETS, MD, *Icahn School of Medicine at Mount Sinai, New York, New York*

MELISSA QUICK, DO, *Group Health Cooperative, Seattle, Washington*

Significant evidence supports the effectiveness and safety of several complementary or integrative treatment approaches to common primary care problems. Acupuncture is effective in the management of chronic low back pain. Mind-body interventions such as cognitive behavior therapy, yoga, tai chi, qi gong, and music therapy may be helpful for treating insomnia. Exercise can reduce anxiety symptoms. Herbal preparations and nutritional supplements can be useful as first-line therapy for certain conditions, such as fish oil for hypertriglyceridemia, St. John's wort for depression, and *Ginkgo biloba* extract for dementia, or as adjunctive therapy, such as coenzyme Q<sub>10</sub> for heart failure. Probiotic supplementation can significantly reduce the likelihood of antibiotic-associated diarrhea. Physicians should caution patients about interactions, and counsel them about the quality and safety of herbal and nutritional supplements. (*Am Fam Physician*. 2016;94(5):369-374. Copyright © 2016 American Academy of Family Physicians.)

**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 346.

Author disclosure: No relevant financial affiliations.

**A**bout one-third of U.S. adults in 2012 reported that they used complementary therapies in the previous year, according to data from the Centers for Disease Control and Prevention.<sup>1</sup> Studies have shown that 12% to 64% of patients do not disclose this use to their physician.<sup>2</sup> The American Academy of Family Physicians advocates for evidence-based evaluations of integrative medicine to facilitate education, treatment, and counseling of patients.<sup>3</sup> This article will discuss the evidence for eight of the best-studied integrative interventions, which primary care physicians should consider incorporating into their practices (*Table 1*).

The lack of adequate regulation of herbs and supplements by the U.S. Food and Drug Administration makes it difficult for consumers and physicians to be assured of the quality and safety of a specific supplement. When possible, this article recommends specific brands of herbal medicines and nutritional supplements known to be of high quality. Reputable information about the quality of specific herb and supplement brands can be found at Consumer Lab.com (<http://www.consumerlab.com/>) and the U.S. Pharmacopeial Convention

(<http://www.usp.org/dietary-supplements/overview>).

## Acupuncture for Chronic Low Back Pain

Acupuncture is a component of traditional East Asian medicine that involves the insertion of needles at specific points on the body to facilitate the recovery of health. A 2012 meta-analysis of pooled data from 29 studies involving 17,922 patients found that acupuncture was effective for treating chronic low back pain compared with sham acupuncture and no treatment, with a moderate effect size of 0.55.<sup>1,4</sup> Acupuncture also provided significant pain relief compared with sham acupuncture and no treatment in a 2015 systematic review and meta-analysis,<sup>5</sup> and in a 2015 overview of 16 systematic reviews.<sup>6</sup> In general, acupuncture is extremely safe, with the most common risk being transient mild discomfort.

The Joint Commission recently recommended acupuncture as a treatment option for pain management.<sup>7</sup> Acupuncture is most often provided individually by licensed acupuncturists; the practice of community or group acupuncture may reduce costs and improve access. Medical acupuncture courses offer family physicians training in this treatment option.

## Complementary/Integrative Therapies

SORT: KEY RECOMMENDATIONS FOR PRACTICE		
Clinical recommendation	Evidence rating	References
Acupuncture provides benefits for chronic low back pain.	A	4-6
Coenzyme Q <sub>10</sub> is a safe adjunctive therapy in patients with heart failure and may improve clinical outcomes.	B	10, 11
Exercise has a small to moderate effect in reducing symptoms in persons with diagnosed anxiety disorders.	B	13, 15
Fish oil is an effective treatment for hypertriglyceridemia.	C	19-21
<i>Ginkgo biloba</i> extract EGb 761 improves cognition in patients with dementia.	A	26, 27
Cognitive behavior therapy is effective for the treatment of insomnia.	A	30
Music is effective for improving subjective sleep quality in adults with insomnia.	B	33
Movement-oriented mind-body approaches such as yoga, tai chi, and qi gong may be beneficial for sleep, especially in older adults and cancer survivors.	A	32, 34
Probiotic supplementation significantly reduces the incidence of antibiotic-associated diarrhea.	A	35, 36
St. John's wort ( <i>Hypericum perforatum</i> ) benefits patients with mild to moderate depression.	A	39

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

**Table 1. Summary of Indications for Complementary Therapies**

Treatment	Indication	First-line vs. adjunctive	Comments
Acupuncture	Chronic low back pain	First-line	Should be performed by a licensed practitioner
Coenzyme Q <sub>10</sub>	Heart failure	Adjunctive	Dosage is 100 mg three times per day
Exercise	Anxiety	First-line	May be helpful in patients with diagnosed anxiety disorders, those with chronic illness without diagnosed anxiety, and those with depression; aerobic exercise is best studied; 30 minutes three to five times per week seems to be most effective
Fish oil	Hypertriglyceridemia	First-line	Lowers triglyceride levels, but unclear if it reduces cardiovascular events; dosage is 4 g of combined eicosapentaenoic acid/docosahexaenoic acid per day; may have minor gastrointestinal adverse effects; no significant medication interactions
<i>Ginkgo biloba</i>	Dementia	First-line	Use extract standardized to 22% to 27% ginkgo flavonoids; typical dosage is 240 mg per day
Mind-body interventions	Insomnia	First-line	Cognitive behavior therapy is most effective; alternatives include meditation, hypnosis, yoga, and tai chi
Probiotics	Prevention of antibiotic-associated diarrhea	First-line	Start within one to three days of starting antibiotics, and continue for one week after stopping; dosage is 5 to 10 billion colony-forming units per day for children, 10 to 20 billion colony-forming units per day for adults; multiple strains available; not clear which are most effective
St. John's wort	Depression	First-line	Use in mild to moderate depression rather than severe depression; do not use in combination with selective serotonin reuptake inhibitors; significant potential for interactions; occasional gastrointestinal adverse effects

## CoQ<sub>10</sub> as Adjunctive Treatment for Heart Failure

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>), also called ubiquinone, is an antioxidant found in high concentrations in the heart. It has a role in mitochondrial electron transport and in supplying myocardial energy. CoQ<sub>10</sub> concentrations have been inversely related to the severity of systolic and diastolic heart failure,<sup>8</sup> and low plasma CoQ<sub>10</sub> levels may independently predict mortality in patients with heart failure.<sup>9</sup> A 2013 meta-analysis of 13 randomized controlled trials (RCTs) found that CoQ<sub>10</sub> increased net ejection fraction by 3.7%.<sup>10</sup> A 2014 multicenter RCT showed that CoQ<sub>10</sub> added to standard therapy was safe and well tolerated, improved symptoms, and reduced major cardiovascular events in patients with heart failure.<sup>11</sup>

There are multiple formulations of CoQ<sub>10</sub>, and bioavailability depends on the type or preparation, although clinical outcomes have not been assessed in head-to-head trials.<sup>12</sup> The Q-SYMBIO trial used the brand Kaneka Q10 at a dosage of 100 mg three times per day.<sup>11</sup> It was well tolerated with similar or fewer adverse effects vs. placebo. The Kaneka Q10 formulation is available under various brand names, including Jarrow and NatureWise. CoQ<sub>10</sub> is an adjunctive therapy and should not be used alone to treat heart failure.

## Exercise for Anxiety

A recent review of 37 meta-analyses of RCTs and observational studies with a total of 42,264 participants reported that exercise had a small but meaningful average anxiolytic effect size of 0.34 in patients with diagnosed anxiety disorders,<sup>13</sup> similar to the average effect size of 0.37 reported in published antidepressant trials.<sup>14</sup> This effect size increased when only RCTs were included. Most studies evaluated the effect of aerobic exercise, although strength training may be effective as well.<sup>15</sup> Another meta-analysis including only RCTs found an effect size of 0.48 for exercise in reducing anxiety symptoms.<sup>16</sup> A third recent analysis examining a pooled sample of 2,914 sedentary adults with chronic illness but no specific anxiety diagnosis found a smaller but still meaningful mean effect size of 0.29.<sup>15</sup> Although the dose, type, and frequency of exercise most effective for specific anxiety conditions are unclear, 30 minutes of aerobic exercise three to five times per week seems reasonable, given current physical activity guidelines. Exercise may also have a modest benefit in treating depression, with an effect size ranging from 0.31 to 0.56 in recent reviews.<sup>17</sup>

For patients who are unable to perform vigorous aerobic exercise, *qi gong*—a gentle form of exercise that originated in China and has recently become popular in the West<sup>18</sup>—and *yoga*<sup>15</sup> also show promise in reducing anxiety symptoms.

## Fish Oil for Hypertriglyceridemia

The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oil, have been shown in multiple studies to lower high triglyceride levels.<sup>19-21</sup> EPA/DHA at a dosage of 4 g per day decreases triglyceride levels by 25% to 30%.<sup>19</sup> Adverse effects are rare, with some patients reporting mild gastrointestinal effects, such as reflux with a fishy taste. Fish oil does not have any known interactions, and dosages up to 5 g per day do not increase bleeding risk.<sup>19</sup>

Although elevated triglyceride levels are associated with increased cardiovascular mortality<sup>22</sup> and fish consumption two to four times per week is associated with lower cardiovascular mortality in cohort studies,<sup>23</sup> it is not known if the triglyceride-lowering effect of fish oil decreases cardiovascular events.<sup>24</sup> Given the safety of fish oil, it seems reasonable to consider it as a means to lower triglyceride levels, while recognizing that its effect on patient-centered outcomes must still be determined. Fish oil capsules are available as the prescription drug Lovaza and as generic equivalents, as well as less expensive over-the-counter brands such as Nordic Naturals and Carlson.

## *Ginkgo biloba* for Dementia

*Ginkgo biloba* is an herb whose leaves have been studied extensively for the treatment of Alzheimer- and vascular-type dementias. Its proposed mechanisms of action include preservation and improvement of mitochondrial function, promotion of hippocampal neurogenesis and neuroplasticity, and enhancement of cerebral blood flow.<sup>25,26</sup> The extract EGb 761, a dry extract of the leaves standardized to 22% to 27% ginkgo flavonoids, has been most extensively studied.<sup>27</sup> A meta-analysis of seven RCTs including 2,684 patients with Alzheimer- or vascular-type dementia showed that standard measures of overall cognition and activities of daily living improved in those who received ginkgo extract at 240 mg per day, whereas a daily dosage of 120 mg had no effect.<sup>26</sup> Effect sizes were similar to those of anticholinesterase medications currently approved for the treatment of Alzheimer-type dementia.<sup>25</sup> Adverse effects were infrequent and included headache and dizziness; discontinuation rates were the same between the ginkgo and placebo groups.<sup>27</sup> Many of the clinical trials of ginkgo, as well as the meta-analyses, have been industry-funded or included an author with industry affiliation.

Although there have been some case reports suggesting an association between ginkgo and increased bleeding risk, a 2011 meta-analysis did not find increased bleeding events or changes in coagulation parameters with standardized ginkgo extract EGb 761.<sup>28</sup> Given the specificity

of the *Ginkgo biloba* extract studied in the meta-analyses, it is important to recommend a supplement that matches EGb 761, such as Nature's Way Ginkgold.

An RCT of ginkgo for prevention of dementia showed no benefit.<sup>29</sup> Because of its apparent effectiveness compared with prescription medications and its favorable adverse effect profile, it is reasonable to recommend ginkgo as an alternative first-line treatment for dementia.

### Mind-Body Interventions for Insomnia

Mind-body interventions such as hypnosis, meditation, guided imagery, mindfulness-based stress reduction, cognitive behavior therapy (CBT), biofeedback, yoga, traditional Chinese practices (e.g., qi gong, tai chi), and music therapy represent safe and cost-effective treatment options for insomnia and other sleep-quality disturbances. A 2015 systematic review found that CBT was the most effective mind-body intervention for insomnia.<sup>30</sup> A previous article in *American Family Physician* reviewed CBT for insomnia and various psychiatric disorders (<http://www.aafp.org/afp/2015/1101/p807.html>). CBT can be costly, however, so group-based versions of mindful awareness practices may offer an economical alternative and have been shown to benefit older patients with sleep disturbances.<sup>31</sup> A recent meta-analysis in patients with cancer and insomnia showed that yoga, meditation, hypnosis, mindfulness-based stress reduction, and qi gong have a moderate effect on the improvement of sleep quality for up to three months.<sup>32</sup> A Cochrane review found that listening to music improves sleep quality and is safe and easy to administer.<sup>33</sup> A 2015 systematic review suggested that specific movement-oriented mind-body approaches such as yoga, tai chi, and qi gong may be beneficial for sleep, especially in older adults and cancer survivors.<sup>34</sup>

Familiarity with one or more mind-body interventions will provide physicians with nonpharmacologic treatment options as first-line therapies to improve sleep quality in all patients. However, there are very few data comparing the effectiveness of different interventions for insomnia in specific patient populations; as such, the choice of intervention should be based on physician-patient dialogue and negotiation, as well as cost and availability.

### Probiotics for Prevention of Antibiotic-Associated Diarrhea

A large variety of probiotics are now being used in clinical practice; the most widely used and thoroughly researched are *Lactobacillus* species, *Bifidobacterium* species, and *Saccharomyces boulardii*, a nonpathogenic yeast. A recent

systematic review pooling data from 63 RCTs including 11,811 participants found a 0.58 relative risk of antibiotic-associated diarrhea among participants who supplemented with probiotics, with a number needed to treat of 13.<sup>35</sup> Most studies used *Lactobacillus* species alone or in combination with other species. A second meta-analysis of 34 studies with 4,138 participants found a similar relative risk of 0.53 and a number needed to treat of 8.<sup>36</sup> This preventive effect persisted regardless of probiotic species used, age group, or duration of treatment. For the prevention of *Clostridium difficile*-associated diarrhea, a meta-analysis including 23 trials and 4,213 participants recently found a relative risk of 0.36 in the probiotic group.<sup>37</sup>

The typical recommended dosage of probiotics is 5 to 10 billion colony-forming units per day for children and 10 to 20 billion per day for adults. Additional research is needed to determine which strains are most effective for specific indications; brands include Culturelle, Jarrow, and Nature's Way Primadophilus. Patients should be advised to start probiotic treatment within one to three days of starting antibiotics and continue for one week after stopping. A recent safety review by the Agency for Healthcare Research and Quality that included more than 24,000 participants reported no adverse effects significant enough to require hospitalization.<sup>38</sup>

### St. John's Wort for Depression

Extracts of St. John's wort, or *Hypericum perforatum*, have been evaluated for treatment of depressive symptoms and major depressive disorder in adults. In a 2008 Cochrane review, St. John's wort was found to be more effective than placebo for the treatment of major depression, although most of the studies focused on mild to moderate rather than severe depression.<sup>39</sup> The St. John's wort group had lower dropout rates than other antidepressants and had a good adverse effect profile, similar to that of placebo.<sup>40</sup> The number needed to treat for St. John's wort is 3.5, which is similar to that of prescription antidepressants.<sup>39</sup>

There appear to be minimal differences in effectiveness between various St. John's wort extracts. Patients should be counseled to use extracts that match those studied, such as extracts standardized to 0.3% hypericin. Two examples available in the United States include Perika St. John's wort by Nature's Way and Kira St. John's wort by Enzymatic Therapy. Therapeutic dosages range from 500 to 1,200 mg per day; a commonly recommended dosage is 300 mg three times per day.

The mechanism of action is not entirely clear.<sup>41</sup> Although St. John's wort is generally safe, it is known to cause induction of several cytochrome P450 enzymes,

which can lead to significant interactions. Some examples include the increased metabolism of oral contraceptives, some antibiotics, protease inhibitors, and certain immunosuppressive medications, as well as decreased levels of digoxin.<sup>42</sup> Because of a possible risk of serotonin syndrome due to additive serotonergic effects, concomitant use with selective serotonin reuptake inhibitors should be avoided. A careful medication history is important, as is the use of an interaction checker database that includes herbs and supplements. For patients with mild to moderate depression who prefer not to use conventional antidepressants, St. John's wort is a reasonable first-line treatment.

**Data Sources:** A PubMed search was completed using the key terms relevant for each treatment and condition pair. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. We also used the following additional databases: the Cochrane database; the National Center for Complementary and Integrative Health database of systematic reviews (<https://nccih.nih.gov>); the Natural Medicines Comprehensive Database; and DynaMed. Search dates: August 1, 2015, to January 26, 2016.

## The Authors

**BENJAMIN KLIGLER, MD, MPH**, is an associate professor in the Department of Family and Community Medicine at Icahn School of Medicine at Mount Sinai, New York, NY.

**RAYMOND TEETS, MD**, is an associate professor in the Department of Family and Community Medicine at Icahn School of Medicine at Mount Sinai.

**MELISSA QUICK, DO**, is a family physician at Group Health Cooperative, Seattle, Wash.

*Address correspondence to Benjamin Kligler, MD, MPH, Icahn School of Medicine at Mount Sinai, 245 Fifth Ave., 2nd Floor, New York, NY 10016 (e-mail: [bkligler@chpnet.org](mailto:bkligler@chpnet.org)). Reprints are not available from the authors.*

## REFERENCES

- Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002–2012. National Health Statistics Reports. February 10, 2015. <http://www.cdc.gov/nchs/data/nhsr/nhsr079.pdf>. Accessed March 8, 2016.
- Robinson A, McGrail MR. Disclosure of CAM use to medical practitioners: a review of qualitative and quantitative studies. *Complement Ther Med*. 2004;12(2-3):90-98.
- American Academy of Family Physicians. Integrative medicine. <http://www.aafp.org/about/policies/all/integrative-medicine1.html>. Accessed January 16, 2016.
- Vickers AJ, Cronin AM, Maschino AC, et al.; Acupuncture Trialists' Collaboration. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med*. 2012;172(19):1444-1453.
- Yuan QL, Guo TM, Liu L, Sun F, Zhang YG. Traditional Chinese medicine for neck pain and low back pain: a systematic review and meta-analysis. *PLoS One*. 2015;10(2):e0117146.
- Liu L, Skinner M, McDonough S, Mabire L, Baxter GD. Acupuncture for low back pain: an overview of systematic reviews. *Evid Based Complement Alternat Med*. 2015;2015:328196.
- The Joint Commission. Clarification of the pain management standard. [http://www.jointcommission.org/clarification\\_of\\_the\\_pain\\_management\\_standard/](http://www.jointcommission.org/clarification_of_the_pain_management_standard/). Accessed September 27, 2015.
- Molyneux SL, Florkowski CM, George PM, et al. Coenzyme Q10: an independent predictor of mortality in chronic heart failure. *J Am Coll Cardiol*. 2008;52(18):1435-1441.
- Folkers K, Vadhanavikit S, Mortensen SA. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. *Proc Natl Acad Sci U S A*. 1985;82(3):901-904.
- Fotino AD, Thompson-Paul AM, Bazzano LA. Effect of coenzyme Q<sub>10</sub> supplementation on heart failure: a meta-analysis. *Am J Clin Nutr*. 2013;97(2):268-275.
- Mortensen SA, Rosenfeldt F, Kumar A, et al.; Q-SYMBIO Study Investigators. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *JACC Heart Fail*. 2014;2(6):641-649.
- DiNicolantonio JJ, Bhutani J, McCarty MF, O'Keefe JH. Coenzyme Q10 for the treatment of heart failure: a review of the literature. *Open Heart*. 2015;2(1):e000326.
- Wegner M, Helmich I, Machado S, Nardi AE, Arias-Carrion O, Budde H. Effects of exercise on anxiety and depression disorders: review of meta-analyses and neurobiological mechanisms. *CNS Neurol Disord Drug Targets*. 2014;13(6):1002-1014.
- Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252-260.
- Herring MP, O'Connor PJ, Dishman RK. The effect of exercise training on anxiety symptoms among patients: a systematic review. *Arch Intern Med*. 2010;170(4):321-331.
- Wipfli BM, Rethorst CD, Landers DM. The anxiolytic effects of exercise: a meta-analysis of randomized trials and dose-response analysis [published correction appears in *J Sport Exerc Psychol*. 2009;31(1):128-129]. *J Sport Exerc Psychol*. 2008;30(4):392-410.
- Rimer J, Dwan K, Lawlor DA, et al. Exercise for depression. *Cochrane Database Syst Rev*. 2012;(7):CD004366.
- Wang CW, Chan CH, Ho RT, Chan JS, Ng SM, Chan CL. Managing stress and anxiety through qigong exercise in healthy adults: a systematic review and meta-analysis of randomized controlled trials. *BMC Complement Altern Med*. 2014;14:8.
- Roth EM. ω-3 carboxylic acids for hypertriglyceridemia. *Expert Opin Pharmacother*. 2015;16(1):123-133.
- Weitz D, Weintraub H, Fisher E, Schwartzbard AZ. Fish oil for the treatment of cardiovascular disease. *Cardiol Rev*. 2010;18(5):258-263.
- Nestel P, Clifton P, Colquhoun D, et al. Indications for omega-3 long chain polyunsaturated fatty acid in the prevention and treatment of cardiovascular disease. *Heart Lung Circ*. 2015;24(8):769-779.
- Liu J, Zeng FF, Liu ZM, Zhang CX, Ling WH, Chen YM. Effects of blood triglycerides on cardiovascular and all-cause mortality: a systematic review and meta-analysis of 61 prospective studies. *Lipids Health Dis*. 2013;12:159.
- Zheng J, Huang T, Yu Y, Hu X, Yang B, Li D. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. *Public Health Nutr*. 2012;15(4):725-737.
- Weintraub H. Update on marine omega-3 fatty acids: management of dyslipidemia and current omega-3 treatment options. *Atherosclerosis*. 2013;230(2):381-389.
- von Gunten A, Schlaefke S, Überla K. Efficacy of *Ginkgo biloba* extract EGB 761 in dementia with behavioural and psychological symptoms: a systematic review. *World J Biol Psychiatry*. Published online ahead of print July 30, 2015. <http://www.tandfonline.com/doi/pdf/10.3109/15622975.2015.1066513>. Accessed March 8, 2016.
- Gauthier S, Schlaefke S. Efficacy and tolerability of *Ginkgo biloba* extract EGB 761 in dementia: a systematic review and meta-analysis of randomized placebo-controlled trials. *Clin Interv Aging*. 2014;9:2065-2077.

## Complementary/Integrative Therapies

27. Weinmann S, Roll S, Schwarzbach C, Vauth C, Willich SN. Effects of *Ginkgo biloba* in dementia: systematic review and meta-analysis. *BMC Geriatr.* 2010;10:14.
28. Kellermann AJ, Kloft C. Is there a risk of bleeding associated with standardized *Ginkgo biloba* extract therapy? A systematic review and meta-analysis. *Pharmacotherapy.* 2011;31(5):490-502.
29. Vellas B, Coley N, Ousset PJ, et al.; GuidAge Study Group. Long-term use of standardised *Ginkgo biloba* extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. *Lancet Neurol.* 2012;11(10):851-859.
30. Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunningham D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Ann Intern Med.* 2015;163(3):191-204.
31. Black DS, O'Reilly GA, Olmstead R, Breen EC, Irwin MR. Mindfulness meditation and improvement in sleep quality and daytime impairment among older adults with sleep disturbances: a randomized clinical trial. *JAMA Intern Med.* 2015;175(4):494-501.
32. Chiu HY, Chiang PC, Miao NF, Lin EY, Tsai PS. The effects of mind-body interventions on sleep in cancer patients: a meta-analysis of randomized controlled trials. *J Clin Psychiatry.* 2014;75(11):1215-1223.
33. Jespersen KV, Koenig J, Jennum P, Vuust P. Music for insomnia in adults. *Cochrane Database Syst Rev.* 2015;(8):CD010459.
34. Neuendorf R, Wahbeh H, Chamine I, Yu J, Hutchison K, Oken BS. The effects of mind-body interventions on sleep quality: a systematic review. *Evid Based Complement Alternat Med.* 2015;2015:902708.
35. Hempel H, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA.* 2012;307(18):1959-1969.
36. Videlock EJ, Cremonini F. Meta-analysis: probiotics in antibiotic-associated diarrhoea. *Aliment Pharmacol Ther.* 2012;35(12):1355-1369.
37. Goldenberg JZ, Ma SS, Saxton JD, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev.* 2013;(5):CD006095.
38. Hempel S, Newberry S, Ruelaz A, et al. Safety of probiotics to reduce risk and prevent or treat disease. Evidence reports/technology assessments no. 200. Rockville, Md.: Agency for Healthcare Research and Quality; 2011.
39. Linde K, Berner MM, Kriston L. St John's wort for major depression. *Cochrane Database Syst Rev.* 2008;(4):CD000448.
40. Kasper S, Gastpar M, Müller WE, et al. Efficacy of St. John's wort extract WS 5570 in acute treatment of mild depression: a reanalysis of data from controlled clinical trials. *Eur Arch Psychiatry Clin Neurosci.* 2008;258(1):59-63.
41. Farahani MS, Bahrami Soltani R, Farzaei MH, Abdollahi M, Rahimi R. Plant-derived natural medicines for the management of depression: an overview of mechanisms of action. *Rev Neurosci.* 2015;26(3):305-321.
42. Shi S, Klotz U. Drug interactions with herbal medicines. *Clin Pharmacokinet.* 2012;51(2):77-104.