ALTERNATIVE MEDICINE ALERT®

The Clinician's Evidence-Based Guide to Integrative Medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Financial Disclosure
Russell H. Greenfield, MD (executive editor), David Kiefer, MD (peer reviewer), and Leslie Coplin (managing editor) have no financial relationships with companies having ties to the material presented in this continuing education program.

Alternative Medicine Alert
is available on-line.
For more information, go to www.ahcmedia.com/online.html or call (800) 688-2421.

Integrative Therapies for Erectile Dysfunction

By Luke Fortney, MD

Dr. Fortney is Assistant Professor, University of Wisconsin-Madison, Department of Family Medicine; he reports no financial relationship to this field of study.

ERECTILE DYSFUNCTION (ED) IS THE MOST COMMON SEXUAL PROBLEM IN men, affecting up to one-third at some point in their lives. It is defined as the inability to achieve or maintain a sufficient erection for satisfactory sex. The prevalence of ED increases with age[1] and is associated with poor cardiovascular health, psychosocial factors, hormonal disorders, recreational drug abuse, and adverse effects from prescribed medications. Anatomic, traumatic, or infectious causes are less commonly involved.[2]

Etiology

Normally, an erection is stimulated by a combination of neurovascular, hormonal, psychological, and situational factors beginning with sexual interest and desire. Through parasympathetic activation, endothelial cells are directly activated to produce nitric oxide (NO), which relaxes endothelial smooth muscle and engorges the corpus cavernosum with arterial blood while venous return is simultaneously restricted.[3]

An integrative approach views the presentation of ED as an opportunity to improve health and reverse the progression of cardiovascular disease, which is the main risk factor for ED. As such, the evaluation and treatment of ED should be sensible, safe, and start with lifestyle. The World Health Organization and American Urological Association recommend using the five-item International Index of Erectile Function Questionnaire (IIEF-5) to assess the patient's concerns and symptoms, and as a precursor to determining treatment options and expectations.[4] An integrative approach should begin by identifying those contributing factors that interfere with the body's optimal functioning and natural healing processes. Several classes of medications and substance abuse — particularly alcohol, tobacco, and marijuana — are common culprits.[5] Blood pressure, BMI, and weight/abdominal girth measurements are quick but sensitive tools that assess and monitor cardiovascular health.

Lifestyle Modification

There is a strong association between chronic diseases of lifestyle and ED, and it is essential that treatment emphasize weight loss, healthy nutrition, and regular exercise.[2,5] Research shows that men with ED are at significant risk for cardiovascular disease.[6-11] One study found that ED symptoms present on average 3 years earlier than symptoms of coronary artery disease.[10] Conversely, adequate blood pressure control is associated with a lower prevalence of ED, particularly in older patients.[11] Similarly, metabolic syndrome seems to play an important role in the etiopathogenesis of ED.[6] For men diagnosed with diabetes mellitus, ED prevalence is as high as 89%.[12,13] Further, both obesity and smoking nearly double the risk of ED,[1,12,14] and alcoholism is a well-known contributor to ED symptoms.[15] Identifying ED presents the opportunity to use an integrative medicine approach that strongly emphasizes healthy lifestyle and mind-body modifications.[12,16] One study found that men who seek treatment for ED may prefer alternatives such as lifestyle changes to pharmaceutical intervention.[17] Even though there is no validated exercise or nutrition regimen that specifically treats ED, exercise and nutrition should be tailored to each patient's specific needs without being extreme, heavily restrictive, or overwhelming. Other lifestyle recommendations include regular dental care, such as flossing, which may be beneficial for prevention of cardiovascular disease and ED.[18] In addition, prolonged (more than 3 hours weekly) or frequent bike riding may inhibit neurovascular flow to the perineum, thereby negatively influencing ED. In these patients, a trial of rest, change in exercise routine, or cycling adaptations — such as a split seat or recumbent posture — can be tried.

For those men lacking organic etiology of ED as determined through medical evaluation, psycho-social-spiritual interventions should be pursued skillfully. It is important to recognize that sexual desire, arousal, and climax are mediated through complex psychoneurological mechanisms. Triggers and causes of ED symptoms can include anxiety, depression, PTSD, excessive worry and guilt, sex abuse history, relationship strain, performance anxiety, postsurgical adjustment disorder, and many other general stresses.[19-23] Although psychological interventions are recognized as a SORT (Strength of Recommendation Taxonomy) category B for ED, there is insufficient evidence to specifically recommend art therapy, hypnosis, aromatherapy, meditation, or guided imagery.[19] However, appropriate methods that enhance the relaxation response and encourage self-reflection should be adapted individually and encouraged as needed.[16,22]

Pharmaceutical Treatments

Targeted pharmaceutical options begin with phosphodiesterase (PDE5) inhibitors such as sildenafil, vardenafil, and tadalafil, which are widely recognized as SORT category A first-line treatment options for ED.[24] Even though PDE5 inhibitors are generally safe, effective, and well tolerated,[25] approximately one-third of men do not respond to them. Prescriptions should include warnings about prolonged and painful erections, worsening or development of Peyronie's symptoms, and other drug interaction precautions. It also must be clarified that these agents are not considered effective for improving libido.[26] However, PDE5 activity is testosterone dependent — research data show that testosterone supplementation in hypogonadism (prevalence 5%-15%) is superior to placebo in improving erections, sexual function, and libido.[27-29] Testosterone supplementation with either compounded bioidentical testosterone or pharmaceutical brands should be used cautiously and monitored regularly by a physician. Further escalation of treatment for unique or refractory cases may rely on the self-administered prostaglandin E1 agent alprostadil.

Herbal and Dietary Supplements

In general, supplements are less effective for treating ED when compared to pharmaceutical options.[30] Further, in 2007, the FDA issued a statement warning consumers to avoid use of impotence supplements.[31] Health care providers should counsel patients to avoid e-mail promotions and Internet advertisements for these and other products that falsely claim to enhance male libido and sexual function. Many of these products are contaminated or adulterated and are not considered reliable or safe for use.[32,33]

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by AHC Media, a division of Thompson Media Group, LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin
MANAGING EDITOR: Neill Kimball
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Alternative Medicine Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

AHC Media

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
$299 per year (Student/Resident rate: $165).
Add $17.95 for shipping & handling.
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 (Student/Resident rate: $180 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.

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

For CME credit, add $50.

Questions & Comments

Please contact Executive Editor **Leslie Coplin**, at leslie.coplin@ahcmedia.com.

Table: Example of a Prevention Prescription

- Regular vigorous exercise most days of the week for 30-60 continuous minutes.
- Healthy calorie-controlled anti-inflammatory or Mediterranean diet rich in phytonutrients/antioxidants (organic fruits/vegetables), omega-3-fatty acids, whole grains, nuts/seeds/legumes, filtered water, green or rooibos tea, and limited lean/organic meats.
- Stress reduction through rest, restorative vacation, meditation, breathing exercises, yoga, journaling, sauna, and select manual therapies.
- Healthy sexual relationships, good communication, and regular erections/ejaculations (3x/week).
- Avoidance of tobacco, marijuana, and other illegal/recreational drugs.
- Moderate alcohol consumption (2 drinks or less per day average).
- Avoidance of anti-nutrients such as high fructose corn syrup, trans-fats, artificial sweeteners/colors/preservatives, and highly processed foods.
- Avoidance of pesticides, herbicides, and overuse of chemical/cleaning products.
- Avoid heating or storing food in plastics (to lessen exposure to Bisphenol-A, a known endocrine and hormone disruptor).

Other products may be safe but ineffective.[19,30] However, there is some evidence for the judicious use of high-quality dietary supplements that may be considered in appropriate situations.

Yohimbine is likely the most effective supplement for treating ED; however it has significant interactions with medications. There also are safety concerns in patients with cardiovascular disease, mood disorders, and renal/hepatic disease among others. Yohimbine, although effective, should be avoided for most patients.[30,34-37] L-arginine in combination with pycnogenol has demonstrated additive effectiveness in treating ED when taken in respective doses of 1000 mg and 40 mg three times a day. Response to this treatment may take up to 12 weeks of consistent daily use, and the combination should be used with caution in patients with gout, asthma, vertigo, and concomitant warfarin use.[38-40] *Panax ginseng* (Asian or Korean) 1000 mg three times a day may be helpful, and there are topical creams available that may also help with premature ejaculation.[30,41-43] For men with documented low dehydroepiandrosterone (DHEA) or testosterone levels, DHEA supplementation at 50 mg daily may be helpful in improving ED symptoms. However, treatment response may take up to 24 weeks. Caution should be used in patients with sleep disturbance, bipolar disorder, acne, and gynecomastia. DHEA treatment seems to be more helpful in men who are also diagnosed with hypertension, but less effective in men with diabetes.[44,45] *Ginkgo biloba* has mixed evidence, but 60-120 mg twice a day may be helpful in treating ED due to antidepressant side effects. Ginkgo should be used cautiously with aspirin or warfarin due to potentiating drug interactions.[46,47] Propionyl-L-carnitine also has mixed evidence, but may be most helpful in improving sildenafil effectiveness in men who have undergone prostate surgery when taken at 1000 mg twice a day. It also may be an adjunctive option to support sildenafil response in men with diabetes.[48,49] Other agents, such as epimedium (horny goat weed), saffron, and pomegranate, are considered safe but evidence is lacking for efficacy in ED treatment.[50-54]

Devices

Other treatment and adjunctive integrative approaches include vacuum erection/constriction devices (VED/VCDs). For those men who are comfortable, motivated, and open-minded to this approach, VED/VCDs have shown promise in postsurgical, structural (Peyronie's), and prostate cancer radiation rehabilitation.[55,56] Satisfaction rates for VED/VCD use are higher than 80% when used appropriately, but the device should be avoided in men with severe Peyronie's, sickle cell disease, or other bleeding disorders.[57] Patients who elect this treatment option should be counseled by a trained health care worker experienced with VED/VCDs.

Acupuncture and Traditional Chinese Medicine

Evidence is generally lacking for acupuncture to treat ED.[58] Further, evidence also is lacking for massage, osteopathic and chiropractic manipulation, yoga, energy medicine, physical therapy, and Alexander technique for the specific treatment of ED.[19] However, these and other methods should be adapted individually and encouraged as part of a larger individualized health plan when appropriate.[16] Comprehensive treatment plans that encourage greater overall health and self awareness can be facilitated through Ayurveda, traditional Chinese medicine, and naturopathy. However, there is insufficient evidence to recommend specific treatments within these disciplines for ED, and caution should be used to avoid complex, overstated, and costly treatments. Various detoxification programs also should be approached skeptically.

Conclusion

Although ED is not a life-threatening disease, it does portend underlying health risk and should be approached skillfully. An integrative approach sees the patient as an

active contributor to the treatment process, and strongly emphasizes both mind and body interventions that take the whole person, including beliefs and preferences, into consideration. Treatment of ED starts with the therapeutic relationship and emphasizes lifestyle changes that more appropriately address the root of the problem in which ED symptoms are only a part. Although pharmaceutical agents are effective, other options should also be considered when appropriate. Caution should be used regarding supplements, particularly those brands that are not verified or third-party tested for quality. Safety and multimedia marketing scams for sex enhancement products continue to be problematic and should be avoided. Finally, maintaining communication with timely follow-up is important to ensure that each patient's concerns are being addressed adequately, noting that ED is a sensitive and often missed diagnosis. ■

References

1. Bacon CG, et al. Sexual function in men older than 50 years of age: Results from the health professionals follow-up study. *Ann Intern Med* 2003;139:161-168.
2. Montague DK, et al. Chapter 1: The management of erectile dysfunction: An AUA update. *J Urol* 2005;174:230-239.
3. Kim NN. Vascular physiology of erectile function. In: Kirby R, et al, eds. *Textbook of Erectile Dysfunction*. 2nd ed. New York: Informa Healthcare USA; 2009: 35-41.
4. Rosen RC, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999;11:319-326.
5. McVary KT. Clinical practice. Erectile dysfunction. *N Engl J Med* 2007;357:2472-2481.
6. Aktas BK, et al. Impact of metabolic syndrome on erectile dysfunction and lower urinary tract symptoms in benign prostatic hyperplasia patients. *Aging Male* 2010;14:48-52.
7. Kostis JB, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005;96:313-321.
8. Thompson IM, et al. Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005;294: 2996-3002.
9. Chew KK, et al. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: Findings from a linked-data study. *J Sex Med* 2010;7:192-202.
10. Inman BA, et al. A population-based longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc* 2009;84:108-113.
11. Cordero A, et al. Erectile dysfunction may improve by blood pressure control in patients with high-risk hypertension. *Postgrad Med* 2010;122:51-56.
12. Holden CA, et al. Windows of opportunity: A holistic approach to men's health. *MJA* 2010;192:708-711.
13. el-Rufaie OE, et al. Sexual dysfunction among type II diabetic men: A controlled study. *J Psychosom Res* 1997;43:605-612.
14. Johannes CB, et al. Incidence of erectile dysfunction in men 40 to 69 years old: Longitudinal results from Massachusetts male aging study. *J Urol* 2000;163:460-463.
15. Dissiz M, Oskay UY. Evaluation of sexual functions in Turkish alcohol-dependent males. *J Sex Med* 2010;doi: 10.1111/j.1743-6109.2010.02091.
16. Fortney L, et al. Introduction to integrative primary care: The health-oriented clinic. *Prim Care* 2010;37:1-12.
17. Wentzell E, Salmeron J. You'll "get viagraed:" Mexican men's preference for alternative erectile dysfunction treatment. *Soc Sci Med* 2009;68:1759-1765.
18. Zadik Y, et al. Erectile dysfunction might be associated with chronic periodontal disease: Two ends of the cardiovascular spectrum. *J Sex Med* 2009;6:1111-1116.
19. Impotence and related conditions. Levels of scientific evidence for specific therapies. Natural Standard: The Authority on Integrative Medicine. Available at: http://naturalstandard.com/databases/effectiveness/ex/nslink-condition.asp?title=Impotence. Accessed March 22, 2011.
20. Smith JF, et al. Sexual function and depressive symptoms among male North American medical students. *J Sex Med* 2010;7:3909-3917.
21. Shabsigh R, et al. Lack of awareness of erectile dysfunction in many men with risk factors for erectile dysfunction. *BMC Urol* 2010;10:10-18.
22. Melnik T, et al. Psychosocial interventions for erectile dysfunction. *Cochrane Database Syst Rev* 2007;18(3):CD004825.
23. Spark RF, et al. Impotence is not always psychogenic. Newer insights into hypothalamic-pituitary-gonadal dysfunction. *JAMA* 1980;243:750-755.
24. Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. *BJU Int* 2005;96:257-280.
25. Rendell MS, et al. Sildenafil Diabetes Study Group. Sildenafil for treatment of erectile dysfunction in men with diabetes: A randomized controlled trial. *JAMA* 1999;281:421-426.
26. Goldstein I, et al. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998;338:1397-1404.
27. Salom MG, Jabaloyas JM. Testosterone deficit syndrome and erectile dysfunction. *Arch Esp Urol* 2010;63: 663-670.
28. Shabsigh R, et al. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2004;172:658-663.

29. Jain P, et al. Testosterone supplementation for erectile dysfunction: Results of a meta-analysis. *J Urol* 2000;164:371-375.
30. Shamloul R. Natural aphrodisiacs. *J Sex Med* 2010;7: 39-49.
31. U.S. Food and Drug Administration (FDA). FDA Warns Consumers Not to Use Super Shangai, Strong Testis, Shangai Ultra, Shangai Ultra X, Lady Shangai, and Shangai Regular (also known as Shangai Chaojimengnan). Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/default.htm. Accessed March 22, 2011.
32. Cortes-Gonzalez JR, et al. The use of *Butea superba* (Roxb.) compared to sildenafil for treating erectile dysfunction. *BJU Int* 2009;105:225-228.
33. Montorsi F, et al. Effect of yohimbine-trazodone on psychogenic impotence: A randomized, double-blind, placebo-controlled study. *Urol* 1994;44:732-736.
34. O'Mathúna DP. "Herbal viagra" should be shunned. *Altern Med Alert* 2010;13:85-89.
35. Carey MP, Johnson BT. Effectiveness of yohimbine in the treatment of erectile disorder: Four meta-analytic integrations. *Arch Sex Behav* 1996;25:341-360.
36. Ashton AK. Yohimbine in the treatment of male erectile dysfunction. *Am J Psychiatr* 1994;151:1397.
37. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: A systematic review and meta-analysis of randomized clinical trials. *J Urol* 1998;159:433-436.
38. Ledda A, et al. Investigation of a complex plant extract (Prelox) for mild to moderate erectile dysfunction in a randomized, double-blind, placebo-controlled, parallel-arm study. *BJU Int* 2010;106:1030-1033.
39. Stanislavov R, Nikolova V. Treatment of erectile dysfunction with pycnogenol and L-arginine. *J Sex Marital Ther* 2003;29:207-213.
40. Durackova Z, et al. Lipid metabolism and erectile function improvement by Pycnogenol, extract from the bark of *Pinus pinaster* in patients suffering from erectile dysfunction — a pilot study. *Nutr Res* 2003;23:1189-1198.
41. Kim TH, et al. Effects of tissue-cultured mountain ginseng (*Panax ginseng* CA Meyer) extract on male patients with erectile dysfunction. *Asian J Androl* 2009;11:356-361.
42. Choi HK, et al. Clinical study of SS-cream in patients with lifelong premature ejaculation. *Urol* 2000;55: 257-261.
43. Hong B, et al. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: A preliminary report. *J Urol* 2002;168:2070-2073.
44. Reiter WJ, et al. Dehydroepiandrosterone (DHEA) in the treatment of erectile dysfunction: A prospective, double-blind, randomized, placebo-controlled study. *Urol* 1999;53:590-595.
45. Reiter WJ, et al. Dehydroepiandrosterone in the treatment of erectile dysfunction in patients with different organic etiologies. *Urol Res* 2001;29:278-81.
46. Wheatley D. Triple-blind, placebo-controlled trial of *Ginkgo biloba* in sexual dysfunction due to antidepressant drugs. *Hum Psychopharmacol* 2004;19:545-548.
47. Kang BJ, et al. A placebo-controlled, double-blind trial of *Ginkgo biloba* for antidepressant-induced sexual dysfunction. *Hum Psychopharmacol* 2002;17:279-284.
48. Gentile V, et al. Preliminary observations on the use of propionyl-L-carnitine in combination with sildenafil in patients with erectile dysfunction and diabetes. *Curr Med Res Opin* 2004;20:1377-1384.
49. Cavallini G, et al. Acetyl-L-carnitine plus propionyl-L-carnitine improve efficacy of sildenafil in treatment of erectile dysfunction after bilateral nerve-sparing radical retropubic prostatectomy. *Urol Nov* 2005;66:1080-1085.
50. Qinna N, et al. A new herbal combination, Etana, for enhancing erectile function: An efficacy and safety study in animals. *Int J Impot Res* 2009;21:315-320.
51. Dell'Agli M, et al. Potent inhibition of human phosphodiesterase-5 by icariin derivatives. *J Nat Prod* 2008;71:1513-1517.
52. Shamsa A, et al. Evaluation of *Crocus sativus* L. (saffron) on male erectile dysfunction: A pilot study. *Phytomedicine* 2009;16:690-693.
53. Safarinejad MR, et al. An open-label, randomized, fixed-dose, crossover study comparing efficacy and safety of sildenafil citrate and saffron (*Crocus sativus* Linn.) for treating erectile dysfunction in men naïve to treatment. *Int J Impot Res* 2010;22:240-250.
54. Forest CP, et al. Efficacy and safety of pomegranate juice on improvement of erectile dysfunction in male patients with mild to moderate erectile dysfunction: A randomized, placebo-controlled, double-blind, crossover study. *Int J Impot Res* 2007;19:564-567.
55. Bosshardt BJ, et al. Objective measurement of effectiveness, therapeutic success and dynamic mechanisms of the vacuum erection device. *Br J Urol* 1995;75:786-791.
56. Pahlajani G, et al. Vacuum erection devices revisited: Its emerging role in the treatment of erectile dysfunction and early penile rehabilitation following prostate cancer therapy. *J Sex Med* 2010;doi:10.1111/j.1743-6109.2010.018841.x.
57. Baltaci S, et al. Treating erectile dysfunction with a vacuum tumescence device: A retrospective analysis of acceptance and satisfaction. *Br J Urol* 1995;76:757-760.
58. Lee MS, et al. Acupuncture for treating erectile dysfunction: A systematic review. *BJU Int* 2009;104:366-370.

Can We Increase Patient Adherence with Intermittent Dosing?

By David Kiefer, MD

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

HAVING JUST GLANCED IN THE REFRIGERATOR AND REALIZED that, yet again, a week had passed and I had forgotten to take my omega-3 capsules, I wondered what I could do to develop a daily routine that would foster my good health. I am not alone in these musings and frustrations; patients recount to me daily that "Sorry, doc, I've been bad," or "I forgot to take my pills last night. I'm sure that's why my blood pressure is up."

For example, from a recent clinic visit, Mr. Jones, in his 70s, presented with a diagnosis of prostate cancer from 3 years ago. After prostatectomy, having declined both radiation therapy and leuprolide, he was closely followed by his urologist with serial testing of prostate-specific antigen. He read about and started himself on a combination of eight dietary supplements, then consulted a naturopathic physician specializing in prostate health who added two additional herbal medicines to his regimen. Several months later, the patient's main complaint was that he only takes his vitamins, herbs, and prescription medications sporadically, finding it difficult to get into a routine, even with the use of a pill box and the placement of the bottles in a conspicuous place in his bathroom. He understood that he would likely have better health outcomes with the regular ingestion of his supplements, but still found it difficult to achieve 100% adherence. Does this sound familiar from your own clinical practice?

We're inundated with tasks to do every day, from flossing teeth, to eating five servings of fruits and veggies, to popping our pills morning, noon, and night. It's not easy to remember all of this with perfect accuracy. An argument could be made that humans are hard-wired for more sporadic behavior: Our ancestors probably ate certain foods when they were available, and then moved on to the next food supply, akin more to a feast-and-famine approach to life rather than a steady routine. Is this still relevant today, possibly indicating that intermittent health interventions are more likely to translate into optimal health? Wouldn't once monthly treatments be easier for all of us than once, twice, or three times daily? What does the research say?

This article will review the literature relevant to patient adherence, including strategies thought to improve adherence, as well as any studies relevant to the benefits or risks of alternatives to daily dosing regimens. As will become apparent later in this article, simply changing the dosing schedule only addresses one aspect of patient adherence, the optimization of which necessarily involves patient factors, provider factors, and aspects of the health care system as a whole (i.e., barriers to care and costs). Nonetheless, dosing regimens are an easily manipulated variable, apparent to both providers and patients, and so of particular interest in this topic.

Background

As a preface to any scientific discussion of patient adherence, it is important to realize that there are challenges in this field, primarily because many of the results are dependent on the methods used to collect the data[1,2]; ways of measuring adherence vary considerably between studies, as do ways of identifying people at risk of nonadherence and who might be amenable to interventions.[3] For example, there are direct methods of measuring adherence, such as observed therapy (thought to be very accurate), and indirect methods, such as pill counts, easy to perform but less accurate.[1,4]

That said, there are several terms used in the medical literature to describe the phenomenon by which patients do or do not behave according to how their health care provider wishes. The most common two terms used are adherence and compliance, the latter falling out of favor because it implies that patients passively follow (or ignore) a provider's treatment plan without any engagement or relationship with the provider in its development.[4] One oft-cited definition of adherence is "…the extent to which a person's behavior — taking medication, following a diet, and/or executing lifestyle changes — corresponds with agreed recommendations from a health care provider."[5] Regardless of the precise definition, there is a concern among researchers and clinicians about stigmatizing patients who are noncompliant or nonadherent, affecting their future interaction with the health care establishment.

Adherence rates vary, but have been reported to be 43%-78% for chronic conditions,[4] though adherence rates between 4%-100% (median 76%) were reported by one review of 569 clinical trials.[1] Medication adherence rates are estimated to be 26%-59% in older adults,[6] approximately 50% in children with chronic illness,[7] > 50% in chronic obstructive pulmonary disease (COPD),[8] and 40%-60% in people with ulcerative colitis.[3] An acceptable adherence rate is often deemed to be 80%, but some researchers prefer to reach 95% for serious medical conditions such as infection with human immunodeficiency virus.[4]

Benefits of Adherence

There are reasons to pay attention to patient adherence. For many medical conditions, patient adherence di-

rectly correlates with decreased morbidity and mortality.[5] On the flip side, poorer adherence rates are associated with the worsening of disease and poorer prognoses, increased health care costs (as much as $100-$300 billion annually), higher hospital admission rates, and even death.[4-6,8,9] Adherence to medication protocols is considered to be one of the most important and modifiable aspects of chronic disease management.[6,10] One review of 19,000 patients from 63 studies found that 26% more patients had a good outcome if they adhered to their provider's recommendations when compared to people who didn't adhere to the recommended medical treatment.[11]

Strategies to Improve Adherence

As we strategize how to improve the likelihood that patients will follow through on treatment recommendations, it is useful to think about barriers that exist to 100% adherence. Part of this involves identifying the root causes of nonadherence, and addressing patients' attitudes and beliefs that may be involved.[3,8] Some patients may be nonadherent merely because of forgetfulness or lack of information, though emotional factors, overly complex regimens, and poor provider communication also may be involved.[4] In addition, not all approaches will be effective for all medical conditions or demographics, as demonstrated in one recent overview of 37 systematic reviews.[12] That said, there are some general trends and specific successes identified in adherence research that are insightful (*see Table 1*), and one research team argues that with a variety of interventions it is possible to increase adherence by 4%-11%.[9]

One meta-analysis compiled results from 33 research trials examining the effect sizes (ES) of interventions to increase adherence to medications in a total of 11,827 adults with a median age of 60 years.[6] The various interventions increased adherence (ES = 0.33) and medication knowledge (ES = 0.48). In particular, medication package changes (including pill boxes), succinct written instructions, stimuli that remind patients to take their medications, dose modification, and having patients monitor medication-related symptoms seemed to make a significant difference in adherence, whereas teaching strategies, and physician medication reviews, interestingly, did not.

Table 1: Strategies to Improve Adherence as per the Medical Literature

- Effective doctor-patient communication, confidence in practitioner's clinical acumen[2,4,8,13]
- Assessing and discussing patients' beliefs and illness perceptions[5,8]
- Proper patient education, including written or visual medication plans; reminding patients[2,4,8]
- Involving patients in treatment plan development (to individualize treatment)[5,8]
- Use once-daily medication for "erratic nonadherence", or the patient who is disorganized and forgets; simplified dosing regimens[4,8,12]
- Self-monitoring and self-management[12]
- Involving allied health care practitioners, including pharmacists[5,12,14]

As mentioned above, there are specific considerations relevant to particular medical conditions or demographics.[1] Management of hypertension remains substandard for many people, and various approaches are recommended to maintain long-term adherence, including changing to once-daily dosing when possible, and carefully monitoring for adverse medication effects as these can be a major deterrent to continued adherence.[15] In children with chronic illnesses, one meta-analysis of 71 studies showed interventions to increase medication adherence were moderately effective (ES approximately 0.40) and yielded health benefits.[7] Approaches generally involved a combination of behavioral, organization, psychological, and educational techniques, though one quarter of the studies used only one strategy to increase adherence; the most effective combination was behavioral and education, yielding better outcomes than either approach alone. Similar benefits with a combination of adherence interventions have been documented for people in need of hemodialysis.[16] For COPD, proper patient education, provider-patient communication, and adjustment of medication dosing have all been shown to aid adherence and health outcomes.[8] Chronic mental illness, such as bipolar disorder and schizophrenia, presents many adherence challenges, some of which can be improved by psychosocial and programmatic interventions, though a recent expert panel found that a switch to long-acting medications or the simplification of the medication regimen could benefit some patients.[17] Adherence to lipid-lowering drugs, especially around the milestone of 6 months after the beginning of therapy, when adherence typically wanes, improves with patient reminders via telephone calls or pharmacist reviews.[2]

It is important to point out that adherence to a particular therapeutic intervention is not always a good thing. For example, we would not want patients to be adherent to a regimen that was imprecise, or incorrect and toxic.[1] Hopefully situations in which it is ideal to be nonadherent are the exception, not the rule, focusing health care providers again on how to improve adherence.

A recent Cochrane review summarized eight patient-oriented interventions for improved adherence.[12] There is some overlap between the categories for a few of the interventions (e.g., self-monitoring may be both "supporting behavior change" and "minimizing risks and harms;" *see Table 2*).

Table 2: Breakdown of Adherence Interventions and Their Effectiveness as per one Cochrane Review

Intervention	Effectiveness
Providing information or education	Insufficient evidence when used alone; with other approaches, mixed evidence
Supporting behavior change	Self-management, self monitoring, and simplified dosing regimens are effective
Acquiring skills and competencies	Mixed results
Support	Some positive results when used alone
Facilitating decision making and communication	Evidence for education and enhanced follow-up, but not for psychosocial interventions
Minimizing risks and harms	Some evidence for efficacy
Improving quality	Financial incentives and changing coordination of care may be effective
Consumer system participation	Insufficient evidence

Intermittent Dosing

Finally returning to the premise of the initial patient case and the possible role of intermittent dosing in improved health outcomes, what do the data show? As mentioned above, simplification of medication regimens to improve adherence is a common conclusion from clinical trials and meta-analyses. Health care providers can simplify medications by changing to once-daily dosing, avoiding polypharmacy, using pill boxes, and incorporating dosing reminders into patient care, among other strategies. However, the literature is interestingly mute about medication adherence and intermittent or sporadic dosing. Of course, this is partly or completely due to the fact that only a few interventions are relevant to this issue. For example, with respect to appropriate use of contraception, there are clearly adherence benefits to once-weekly patches or every three month medroxyprogesterone injections over daily oral contraceptives; benefits from other longer-term options such as the intrauterine device or intradermal etonogestrel every three years are corroborated by the medical literature.[18] Other examples of intermittently dosed pharmaceuticals are weekly or monthly dosing of bisphosphonates for osteoporosis and depot formulations of medications for prostate cancer. One review of the topic found 8.8%-12.0% higher adherence and higher patient preference for once-weekly dosed medications as compared to once-daily dosing in 11 studies.[10] Once-monthly medications had similar adherence to once-daily medications, but this conclusion was based on only one head-to-head trial. This review brought up a very important concern specific to intermittent dosing: There is a greater risk of significant undertreatment and associated therapeutic ineffectiveness associated with missing one dose of a once-weekly medication vs missing one daily medication, and there is the increased chance of toxicity if patients attempt to make up for missed doses of intermittently dosed medications by taking extra doses.

In the realm of integrative medicine, there are a few examples of official recommendations that venture away from daily dosing, perhaps leading to a higher adherence benefit for this treatment approach. For example, repletion of vitamin D insufficiency with 50,000 IU once weekly of orally dosed vitamin D2 is practically standard of care,[19] as is the prescription of twice-weekly fish intake for cardiovascular health.[20] In addition, and thankfully for some of our patients, it is not necessary to exercise daily; rather "most days of the week" activity is sufficient for cardiovascular conditioning and weight loss. The new frontier of medicine may very well be epigenetics, and initial findings may have relevance for the issue of dietary supplements and nutrition, and regularity of dosing. One preliminary study noted that the ingestion of one cup of broccoli sprouts led to maintained hyperacetylation of histone (an epigenetic anticancer effect) in peripheral blood mononuclear cells for 48 hours.[21] Does this mean that we only need to eat such vegetables every 2-3 days to receive optimal anticancer benefits? Perhaps, but such conclusions are still very premature and need to be corroborated.

Conclusion

The literature on patient adherence is extensive, providing many details about causes of nonadherence and approaches to maximize follow-through on medical treatment recommendations. Such strategies are extremely important; improved patient adherence absolutely correlates with better health outcomes on any of a variety of scales and measurements. Strategies to improve adherence should be tailored to each individual patient and diagnosis, and the best results usually incorporate a variety of approaches from improved provider communication to patient education and the simplification of medication regimens. Data on medication dosing definitely show improved patient adherence with once-daily dosing, and likely once-weekly dosing as per one literature review. There are some lifestyle, supplement, and nutrition rec-

ommendations that show health benefits when dosed intermittently, though the research remains to be done to show that these lead as well to improved adherence.

Recommendation

Improving patient adherence needs to be on the forefront of all clinician's minds, whether it involves medication prescriptions or the recommendation of complementary and alternative therapeutics. Many strategies exist that lead to an improvement in adherence, and therefore, health outcomes. One of these is the simplification of a patient's medication regimen, once-daily or even once-weekly being the preferred dosing frequency. As long as efficacy of a reduced dosing frequency has been ensured through clinical trials, realizing that this may not yet have been established for many dietary supplements, all clinicians should opt for supplement, medication, or lifestyle interventions that might be effective while requiring less frequent dosing strategies. ■

References

1. DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Med Care* 2004;42:200-209.
2. Schedlbauer A, et al. Interventions to improve adherence to lipid lowering medication. *Cochrane Database Syst Rev* 2010, Issue 3. Art. No.: CD004371.
3. Kane SV, Robinson A. Review article: Understanding adherence to medication in ulcerative colitis — innovative thinking and evolving concepts. *Aliment Pharmacol Ther* 2010;32:1051-1058.
4. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-497.
5. Sabaté E. Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization; 2003.
6. Conn VS, et al. Interventions to improve medication adherence among older adults: Meta-analysis of adherence outcomes among randomized controlled trials. *Gerontologist* 2009;49:447-462.
7. Graves MM, et al. The efficacy of adherence interventions for chronically ill children: A meta-analytic review. *J Pediatr Psychol* 2010;35:368-382.
8. Lareau SC, Yawn BP. Improving adherence with inhaler therapy in COPD. *Int J Chron Obstruct Pulmon Dis* 2010;5:401-406.
9. Peterson AM, et al. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health System Pharm* 2003;60:657-665.
10. Kruk ME, et al. The relation between intermittent dosing and adherence: Preliminary insights. *Clin Ther* 2006;28:1989-1995.
11. DiMatteo MR, et al. Patient adherence and medical treatment outcomes: A meta-anlaysis. *Medical Care* 2002;40:794-811.
12. Ryan R, et al. Consumer-oriented interventions for evidence-based prescribing and medicines use: An overview of systematic reviews. *Cochrane Database Syst Rev* 2011;5:CD007768.
13. Zolnierek KB, Dimatteo MR. Physician communication and patient adherence to treatment: A meta-analysis. *Med Care* 2009;47:826-834.
14. Morgado MP, et al. Pharmacist interventions to enhance blood pressure control and adherence to antihypertensive therapy: Review and meta-analysis. *Am J Health Syst Pharm* 2011;68:241-253.
15. Galzerano D, et al. Do we need more than just powerful blood pressure reductions? New paradigms in end-organ protection. *Vasc Health Risk Manag* 2010;6:479-494.
16. Matteson ML, Russell C. Interventions to improve hemodialysis adherence: A systematic review of randomized-controlled trials. *Hemodial Int* 2010;14:370-382.
17. Velligan DI, et al. Strategies for addressing adherence problems in patients with serious and persistent mental illness: Recommendations from the expert consensus guidelines. *J Psychiatr Pract* 2010;16:306-324.
18. Zibners A, et al. Comparison of continuation rates for hormonal contraception among adolescents. *J Pediatr Adolesc Gynecol* 1999;12:90-94.
19. Holick MF. The vitamin D epidemic and its health consequences. *J Nutr* 2005;135:2739S-2748S.
20. Covington MB. Omega-3 fatty acids. *Am Fam Physician* 2004;70:133-140.
21. Dashwood RH, Ho E. Dietary histone deacetylase inhibitors: From cells to mice to man. *Semin Cancer Biol* 2007;17:363-369.

Ya Gotta Believe — Expectation and Outcome

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *In a seminal study on the interaction between mind and body, effects of a continuous infusion of a potent opioid on pain sensation were drastically altered as a result of expectation of effectiveness. The study's results bring to the fore the idea that a patient's belief in a given drug therapy has a significant impact on its clinical effectiveness.*

Source #1: Bingel U, et al. The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. *Sci Transl Med* 2011;3:70ra14.

Practitioners and patients alike find comfort in knowing that pharmaceuticals possess agreed-upon physiologic mechanisms of action, such that therapeutic responses are considered reproducible and essentially linear; but there has long been a nagging question regarding whether an individual's expectations regarding a given therapy might influence treatment outcome. Prior data suggest that verbal cues that influence patient expectation actually may alter a drug's therapeutic efficacy.

The authors of this creative, within-subject study investigated the impact of expectation of effectiveness on analgesia provided by the potent μ-opioid receptor agonist remifentanil, which has a rapid onset of action and short elimination half-life (about 10 minutes). Pain perception and analgesia were chosen because the neurobiological mechanisms of both are well described.

Healthy volunteers (n = 22; 7 female; all right-handed; mean age, 28 years; range, 21 to 40 years) were recruited with the understanding that the study aimed to investigate the brain mechanisms responsible for differing levels of response to opioids among individuals. They were told that remifentanil relieves pain quickly when infused intravenously, but can worsen pain when the infusion is stopped.

The study comprised two sessions separated by at least 24 hours, one introductory and one main experimental session that included functional magnetic resonance imaging (fMRI). During the introductory session participants underwent what was called an "expectation manipulation-conditioning procedure" to induce positive and negative treatment expectations. They were exposed to painful heat through a probe applied to the right calf in four sequences: two with an IV infusion of saline, during which participants were asked to describe this baseline experience of pain in the absence of treatment; one with IV infusion of remifentanil, during which participants were told they should expect significant pain relief, but during which, and unbeknownst to the subjects, the heat of the painful stimulus was turned down; and one where the IV infusion of remifentanil was stopped, during which subjects were told to expect a worsening of pain, while in fact the temperature of the heat probe was increased, again unbeknownst to the participants.

The main experimental session consisted of four runs of identical thermal stimulation to the right mid-calf, each including 10 thermal pain stimuli lasting approximately 10 minutes (adjusted to produce a pain intensity rating of 70 on a VAS, where 0 corresponds to "no pain" and 100 to "unbearable pain"). After a baseline run performed with a saline infusion only, the remifentanil infusion was started without the subjects being told, so that in the second run the analgesic effect of 30 minutes of a remifentanil infusion could be assessed without any treatment expectation. To distract from potential psychotropic effects experienced with rising CNS concentrations of remifentanil, a 15-minute structural brain scan was performed and participants were told that the study might cause "vibrations that may evoke a sensation of slight disorientation in some participants." To begin the third or "positive expectancy" run, subjects were told that the infusion "would now be started by the anesthetist." When that infusion was completed, participants were told "the infusion will now be stopped to investigate the possible increase in pain after ceasing the opioid infusion." In reality, the infusion was continued throughout the fourth or "negative expectancy" run.

Whole brain fMRI including the brainstem was used to record brain activity and investigate the neural mechanisms by which expectancy might modulate the efficacy of pharmacological treatment. Activity levels within several regions of the brain previously have been reported to consistently correlate with intensity of nociceptive inputs and resultant pain perception, and were taken as surrogate markers of analgesia.

Other study measures included pain intensity rating, anxiety levels pre- and post-treatment, and overall unpleasantness of the painful stimuli. To minimize potential habituation or sensitization during the course of the experiment, the site of thermal stimulation along the right mid-calf was changed slightly after each of the four runs.

The reported results are compelling: the hidden application of remifentanil without treatment expectancy significantly reduced pain intensity ratings from 66 ± 2 during baseline saline infusion to 55 ± 3 [$t(21) = 5.1$, $P < 0.001$]. Positive expectancy significantly enhanced analgesia, as pain ratings further decreased to 39 ± 3 [$t(21) = 6.4$, $P < 0.001$]. Negative expectancy, when the subjects had been led to believe that the drug was stopped, resulted in a considerable increase in pain intensity from 39 ± 3 (positive expectancy run) to 64 ± 3 (negative expectancy run) [$t(21) = 8.5$, $P < 0.001$]; thus, negative expectancy essentially abolished the analgesic effect of remifentanil, as pain intensity under negative expectancy did not differ from pain intensity during baseline saline infusion [$t(21) = 0.68$, $P = 0.5$]. Results for pain unpleasantness ratings showed a similar pattern. The analgesic benefit from positive expectancy was negatively correlated with anxiety ratings obtained at the start of the respective run ($r = -0.55$, $P < 0.01$), indicating that participants who were less anxious showed a greater analgesic benefit of positive expectancy.

The reported subjective effects were substantiated by significant changes in the neural activity in brain regions involved with the coding of pain intensity. Positive expectancy effects were associated with activity in the endogenous pain modulatory system, and negative expectancy effects with activity in the hippocampus.

The authors conclude in their model of pain and analgesia that positive treatment expectancies literally double the analgesic benefit of remifentanil, while negative treat-

ment expectation interferes with the analgesic potential of remifentanil to the point of completely negating it. These effects were paralleled by significant changes in neural responses in core brain regions that are involved in the intensity coding of pain. The researchers close by stating that a patient's expectation of a drug's effect critically influences its therapeutic efficacy, and that regulatory brain mechanisms differ as a function of expectancy.

Synopsis: *In another investigation of the impact of patient confidence in treatment outcome, expectations of recovery at baseline in patients hospitalized for cardiovascular disease were positively associated with both functional capacity and survival over a lengthy follow-up period.*

Source #2: Barefoot JC, et al. Recovery expectations and long-term prognosis of patients with coronary heart disease. *Arch Intern Med* doi:10.1001/archinternmed.2011.41

Duke University researchers studied patients undergoing diagnostic coronary angiography from 1992-1996 found to have clinically significant disease (75% stenosis of 1 coronary artery) in the prospective Mediators of Social Support Study (MOSS). A total of 3737 qualifying patients enrolled, with basic mortality analyses conducted on only 2818 patients (75% of the study population) due to missing information. Coronary artery bypass surgery (CABG) was performed on 1277 of the participants (45.3%) at some point during the follow-up period, with 1156 (41.0%) undergoing percutaneous transluminal coronary angioplasty (PTCA). Of these, both procedures were performed on 396 (14.1% of the sample). The remaining 781 patients (27.7%) were medically treated throughout the course of the study.

The Duke database electronic record was the source of information about comorbidities and relevant health history. Coronary disease severity was controlled in the analyses by including the number of coronary arteries with at least 75% stenosis (1-3), left ventricular ejection fraction, and a 6-level variable indicating the presence and severity of congestive heart failure. These measures were obtained during the baseline angiographic examination. Demographic variables were covaried to control for potential economic and social confounding factors and included education, ethnicity, and marital status.

Study instruments included the Expectations for Coping Scale (ECS) used to determine the patient's expectations regarding future lifestyle and future cardiac prognosis (half of the items were worded so that agreement implied positive expectations, and half were worded in the other direction); the Duke Activity Status Index (DASI) to assess the patient's ability to perform a range of physical activities; the Interpersonal Support Evaluation List (ISEL), designed to measure perceived availability of social support; and the Center for Epidemiologic Studies Depression Scale (CES-D), a measure of the frequency of various depressive symptoms experienced during the previous week.

Follow-up of the patients was conducted at 6 months and 12 months after catheterization and annually thereafter. Telephone interviews were conducted with patients 1 year after hospitalization. DASI scores were obtained for 2392 patients who also had DASI scores at baseline, representing 85% of those in the mortality analyses. Follow-up times for surviving patients averaged 14.6 years and ranged up to 17 years. As of December 2008, 1637 of the 2818 patients had died, with 885 of the deaths classified by an independent committee as being secondary to cardiac causes.

ECS scores indicating positive expectations were associated with reduced mortality risk; unadjusted data showed a mortality rate of 28.8 deaths per 100 patients during the 10 years after baseline for those in the highest quartile of expectations compared with 56.9 deaths per 100 for those in the lowest quartile. For a difference equivalent to an interquartile range of expectations, the hazard ratio (HR) for total mortality was 0.76 (95% confidence interval [CI], 0.71-0.82) and 0.76 (95% CI, 0.69-0.83) for cardiovascular mortality. The HRs were 0.83 (95% CI, 0.76-0.91) and 0.79 (95% CI, 0.70-0.89) with further adjustments for demographic and psychosocial covariates. Similar associations ($P < 0.001$) were observed for functional status.

The authors conclude that in their large cohort of patients with known coronary artery disease, those patients who had more favorable expectations about their likelihood of recovery and return to a normal lifestyle had better long-term survival, as well as better functional status after their hospitalization.

■ COMMENTARY

These two articles are presented jointly because their findings provide the backdrop for broader consideration of the mind–body continuum in clinical care. Add to the current context the findings of Kaptchuk et al (*PLoS ONE* 2010;5:e15591) recently reviewed in *Alternative Medicine Alert* (See February 2011) that showed accessing therapeutic benefits from the placebo effect does not require deception. Considered together these results comprise a formidable basis for the concept that health care practitioners must strive to enlist both a patient's trust in their doctor's clinical acumen as well as comfort with recommended care, invasive or otherwise, to optimize the chances of successful treatment outcome.

Belief is a complex variable encompassing a wide variety of factors including at least personal experience, the

chronic nature of specific health problems, interpersonal relationships (including those with health care providers), mood, coping skills, and the clinical environment. In light of this, on an Olympic scale one might consider the degree of difficulty enlisting a patient's positive expectations to be high, but each of these issues can be addressed by using something almost all healers have at their disposal – their compassionate selves. This should not be considered some New Age concept — it is, in fact, the basis for the healing relationship between practitioner and provider. What this new scientific evidence brings to light is that practitioners probably do not use the healing relationship inherent in the medical encounter to its greatest effect. According to the results of the aforementioned studies, that could translate into treatment failure even when the biochemical and physiologic rationales behind that treatment are secure.

Time is in short supply in present-day practitioner–patient interactions, but when employed efficiently, that time can be used to describe the mechanism of action of a drug or explain a procedure, and at least to underscore our belief as practitioners in the recommended path forward. This may be construed as manipulation, but if a recommendation is made to a patient regarding care, it is reasonable to assume the practitioner making the recommendation believes it could help — sharing that belief, literally couching the intervention in positive terms, may enhance therapeutic efficacy.

To be sure there are some concerns with the two studies reviewed here, not the least of which being the small sample size in the former, and the missing pieces of data in the second trial; regardless, the methodology is otherwise sound and the conclusions persuasive. Expectations and related beliefs have an impact not only on the effect of therapies, but potentially on long-term survival, too.

Medical treatment is most always considered a matter of physiology, but the role of psychology in any cogent treatment plan may soon share center stage. Recall the children's story "Dumbo," where the elephant could not fly without the "magic feather" until the day he lost the feather, only to find he was able to fly by himself all along. Belief is powerful medicine, an underutilized medicine. As these studies show, to do the best by the people who willingly share their life stories with us as practitioners, we must do more than focus solely on the physical — we must engage them in positive expectation wherever appropriate. Not doing so places our patients at a significant disadvantage. ■

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. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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 Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

27. Erections are physiologically mediated through what sequence of events?

a. Sympathetic activation, testosterone release, myosin contraction of the corpus cavernosum
b. Arousal, parasympathetic activation, endothelial release of nitric oxide, engorgement of corpus cavernosum with blood
c. Nitric oxide release from the brain, activation of autonomic nervous system, release of testosterone, engorgement of blood into the corpus spongiosum
d. Parasympathetic and sympathetic activation, testicular release of nitric oxide, endothelial stimulation by arginine

28. Herbs and supplements for erectile dysfunction are always considered safe to use in men with cardiovascular disease who take medications and do not need to be monitored.

a. True
b. False

3. Which of the following directly affects libido?

a. Saffron
b. Arginine
c. Testosterone
d. Sildenafil

In Future Issues:

Vitamin D for Multiple Sclerosis

Melatonin and Menopause

Dear *Alternative Medicine Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) semester and provides us with an opportunity to tell you about **some new procedures for earning CME and quicker delivery of your credit letter.**

Alternative Medicine Alert, sponsored by AHC Media, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours — the best possible patient care.

The objectives of *Alternative Medicine Alert* are:

- 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.

The American Medical Association, which oversees the Physician's Recognition Award and credit system and allows AHC Media to award *AMA PRA Category 1 Credit™*, has changed its requirements for awarding *AMA PRA Category 1 Credit™*. Enduring materials, like this newsletter, are now required to include an assessment of the learner's performance; the activity provider can award credit only if a minimum performance level is met. AHC Media considered several ways of meeting these new AMA requirements and chose the most expedient method for our learners.

HERE ARE THE STEPS YOU NEED TO TAKE TO EARN CREDIT FOR THIS ACTIVITY:

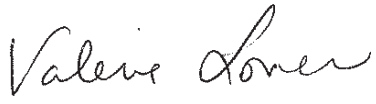
1. Read and study the activity, using the provided references for further research.
2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.*
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.** You will no longer have to wait to receive your credit letter!

This activity is valid 36 months from the date of publication. The target audience for this activity is primary care physicians and internists.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560. You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,



Valerie Loner
Continuing Education Director
AHC Media