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INSIDE

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Can Vitamin D Protect Against Colds and Flus?

By David Kiefer, MD

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Synopsis: *Laboratory science has delineated convincing connections between vitamin D and immune system function, some of which have been borne out in clinical trials on the prevention and treatment of respiratory infections.*

THE CONNECTION BETWEEN VITAMIN D AND BONE HEALTH, AND THE associations with vitamin D deficiency or insufficiency and fractures or falls, has been well investigated in the medical literature. More recent findings, including the presence of a vitamin D receptor (VDR) in many human tissues,[1,2] are pointing to other roles for this vitamin-hormone. With respect to immune system function, there are physiological, observational, and clinical underpinnings for an effect of vitamin D on upper respiratory infection (URI) prevention and, possibly, treatment.

Historical Perspective

As early as the 1800s, a possible connection between vitamin D deficiency and infections was proposed, though the physicians at first had the cause-effect reversed. In 19th and 20th century Europe, the incidence of tuberculosis and pneumonia was found to be significantly higher in people suffering from rickets, or severe vitamin D deficiency; hence, the thought that it was actually the infection that caused the rickets.[1-3] By the 1920s, researchers finally realized that vitamin D in cod liver oil cured rickets, and correctly surmised that it was the deficiency of vitamin D that led to infections. It took many more years to elucidate the mechanism behind that effect.

Observational Data

More recently, researchers have posited that increased incidence and severity of upper respiratory infections with viruses such as influenza, rhinovirus, and respiratory syncytial virus, and

Summary Points

• People with lower serum 25(OH)D are at risk for more severe respiratory disease, but also may respond better to vitamin D supplementation.

• Increased incidence and severity of upper respiratory infections with viruses and pneumococcal infection in the fall and winter may be the result of lower availability of natural vitamin D in winter months.

• Few adverse effects have been report in persons taking supplemental vitamin D.

pneumococcal infection in the fall and winter may, in fact, be due to dropping serum 25-hydroxyvitamin-D (25(OH) D) levels as the amount and intensity of sunlight falls, as much as from the indoor crowding that occurs during those seasons.[3-6] One study found a correlation between serum 25(OH)D and incidence of such infections.[7] In a double-blind fashion, these researchers checked 25(OH) D levels monthly from September to January in 198 adults, asking them to report any symptoms consistent with a viral URI. Complicated statistical analyses done on the clinical symptoms and serum 25(OH)D levels found that a level of 38 ng/mL best differentiated the groups that did or did not develop a viral URI; serum 25(OH)D above 38 ng/mL cut the risk approximately in half ($P < 0.0001$).

The researchers were unable to comment on whether the duration of URIs varied with differing serum 25(OH)D.

A review of data collected during the National Health and Nutrition Examination Survey between 1988-1994 found that the medium serum 25(OH)D was 29 ng/mL and that there was an inverse relationship between serum 25(OH)D and recent URI ($P < 0.001$).[8] People with serum 25(OH)D < 10 ng/mL had the highest rate of URI, but so did people in the 10-30 ng/mL group when compared to > 30 ng/mL. The authors saw some indication of a plateau effect at 30 ng/mL beyond which there would be minimal additional protective effect against URIs, but they said follow-up trials are warranted to further elucidate this.

Some hints from vitamin D research done for other purposes expand on the idea that there might be benefits with respect to viral URI infections; although there can be methodological flaws with this type of retrospective analysis, it is interesting for hypothesis generation. For example, a secondary analysis was done on data collected from a randomized trial of vitamin D for bone mineral density improvements in African American women, showing that the women in the vitamin D group had fewer colds and flus and that these infections, when they did occur, lacked a seasonality.[9] However, other researchers sent questionnaires to women who had completed a trial of vitamin D and/or calcium for the secondary prevention of osteoporotic fractures; the authors did not find a protective effect of vitamin D on URI incidence nor antibiotic use, though they comment on the fact that noncompliance and the nonspecificity of the questions could have accounted for the lack of an association.[10]

Further research found no difference in serum 25(OH) D in Canadian children younger than age 2 admitted for lower respiratory infection when compared to a control group without a history of infection.[11] The authors assert that vitamin D may be more effective against bacterial than viral infections, possibly due to vitamin D's preferential shift toward increasing (Th)-2 rather than (Th)-1; higher levels of T helper cells (Th)-1 seem to correlate with decreased severity of some respiratory virus infections,[11] explaining why a vitamin D and (Th)-2 connection may not translate to efficacy with viral infections. In addition, vitamin D may be a major factor only in cases of severe deficiency; many of the Canadian children in this study were ingesting some vitamin D in formula or as supplements and had mid-range serum 25(OH)D levels.

A different Canadian study in children younger than 5 years old measured 25(OH)D in those admitted to the hospital with lower respiratory infection (n = 105) vs. those presenting with non-respiratory complaints (n = 92), and found similar vitamin D levels: 33 ng/mL vs. 32.5 ng/mL, respectively.[12] However, the subset of children admitted to the intensive care unit (ICU) had 25(OH)D of 19.6 ng/

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mL, significantly lower than the control group ($P = 0.001$) or children admitted just to the general pediatric floor ($P = 0.001$). The researchers conclude that vitamin D deficiency is a risk factor for more severe respiratory disease and ICU admission.

Other observations are that the role of vitamin D in the innate immune system response may explain the higher incidence and increased severity of tuberculosis in African Americans in the United States, a demographic shown to generally have a lower serum 25(OH)D.[13]

Mechanisms of Action

Past reviews in *Alternative Medicine Alert* have detailed the different forms of vitamin D, its metabolites, and relationship to calcium absorption and bone formation. Its immune system effects may, in fact, be as significant and widespread throughout the body. As mentioned above, many tissue types have VDRs, including thymic and bone marrow B and T cells. After the most active form of vitamin D 1,25-dihydroxyvitamin D binds to VDR, transcriptional regulation of numerous proteins occurs, affecting calcium and phosphate metabolism, cell proliferation and differentiation, and immune system function.[1]

There are complicated effects of vitamin D on both the innate and acquired, or adaptive, immune systems (see diagrams in references 1 and 2); overall, most experts consider 1,25-dihydroxyvitamin-D to be a potent "immunomodulator," acting via numerous mechanisms.[13] The specific immune system effects of vitamin D derivatives are numerous and varied (*see Table at right, Specific Immune System Effects of Vitamin D and Associated Mechanisms*).

Human Clinical Trials

The medical literature is rife with attempts to prevent or treat various infections with vitamin D supplementation. Some trials used cod liver oil,[3] known to be a source of vitamin D, vitamin A, and omega-3 fatty acids, but it is difficult to tease out the vitamin D effect from the other nutrients. Research focusing on vitamin D has had a mixture of results, from convincing efficacy or borderline benefit, to no effect, some of which is related to the study population (demographic, baseline vitamin D, etc.) and specific intervention (dose and dosing regimen). Although some research has revisited the tuberculosis-vitamin D connection,[17] this section will focus on those trials specific to URIs.

One review collected the results from 13 trials, 10 of which were placebo-controlled, that addressed vitamin D therapy and clinical outcomes relevant to infectious diseases.[18] The trials varied widely in patient population, age, medical conditions (URIs to schistosomiasis), vitamin D dose, and whether ergocalciferol (D2) or cholecalciferol (D3) was used. The authors were convinced of a role for vitamin D in the prevention and treatment of tuberculosis, influenza, and other viral URIs, though they deferred to future research to refine the details. Furthermore, all future research, they argue, needs to include baseline and follow-up serum 25(OH)D testing, to acknowledge the

Specific Immune System Effects of Vitamin D and Associated Mechanisms

- Increases production of cathelicidin by macrophages and beta-defensin by endothelial cells, peptides that may inactivate viruses[2,3,6,7,14]
- Cytokine modulation, decreasing inflammation and helping to decrease the severity of viral pneumonia[7]
- Monocytes and macrophages exposed to antigens increase VDR gene production[13,14]
- Vitamin D below certain levels (i.e., 20 ng/mL) impedes initiation of the innate immune system response via monocytes and macrophages[13]
- Extrarenal cells, including activated macrophages, express 1alpha-hydroxylase, catalyzing the formation of 1,25-dihydroxyvitamin-D[1,2,6]
- Enhancement of regulatory T cells[6]
- Enhancement of IL-10 production and serum TGF-beta[16]
- Increases production of antimicrobial peptides, such as defensin, in primary human monocytic and epithelial cells[16]
- The defensin peptide retrocyclin-2 inhibits influenza virus by blocking hemagglutinin-mediated membrane fusion[15]
- Reduces inflammation by modulating cytokine release[16]
- Inhibits or enhances (Th)-2 responses and resulting cytokines, depending on cells involved and whether or not cells have been primed by antigen or are naive[6]

30-32 ng/mL threshold level for clinical effect, and to improve on basic methodology.

Other themes surface from a review of individual research trials. For example, in the pediatric realm, a randomized, double-blind, placebo-controlled trial in Japan with intention-to-treat analysis in 430 school children (334 completed the study) used 1,200 IU of vitamin D3 daily from December to March and found that there was a modest decrease in the incidence of seasonal influenza A in the treatment group (RR = 0.36, $P = 0.04$).[16] It could be argued that this intervention started late, given that it can take up to 3 months to reach a steady state of vitamin D after beginning supplementation, and that is what accounted for the results showing only modest effects.

Another trial, this time in 162 adults, showed that 2,000 IU vitamin D3 administered from December to June did not decrease the incidence of URIs when compared to placebo, nor was there any difference in severity or duration of URI symptoms.[15] Baseline serum 25(OH)D was 25 ng/mL (63.7 nmol/L) and increased to 34.7 ng/mL (86.7 nmol/L) after 3 months; these values are close to what is thought to be a "threshold effect" below which minimal, if any, physiological effect is seen. Also, subgroup analyses in this trial show that vitamin D supplementation may have a greater benefit in people with lower baseline values, explaining, perhaps, why some people respond to vitamin D supplementation and others don't. However, researchers have noted that some people have genetic VDR polymorphisms that may lead to decreased expression of VDRs and therefore less vitamin D effect in combating infections.[12] In addition, there is some concern about the research methodology in the above trial, as it is unclear whether an intention-to-treat analysis was undertaken on the 148 people who actually completed the trial.

The negative trials give us some indication about the proper possible use of vitamin D, but efficacy trials are still necessary to definitively establish benefit.

In 164 Finnish military recruits, those who received 400 IU vitamin D daily from October to March were not absent less often from work ($P = 0.096$) but they did have fewer self-reported URIs ($P = 0.045$) than the placebo group.[19] The number-needed-to-treat for this intervention was 6.4, calculated from men without any absences from work. Although there were 60 dropouts over the course of the study, the researchers used intention-to-treat analyses, making the results more accurate and, therefore, believable. The treatment group achieved a serum 25(OH)D of 28.7 ng/mL after 6 months of supplementation, probably not an adequate level for most physiological effects of vitamin, while the placebo group dropped to 20.4 ng/mL. In Afghanistan, 415 children with pneumonia were randomized to receive either one dose of 100,000 IU vitamin D3 orally or placebo.[20] The intervention did not affect the duration of illness but it decreased the number of children with repeat pneumonia in the ensuing 90 days ($P = 0.01$) and lengthened the number of days from 59 to 72 until the next pneumonia ($P = 0.02$). No adverse effects were noted.

Dose

The specifics of dosing was discussed in detail in the July 2010 issue of *Alternative Medicine Alert*. The research described above seems to indicate the importance of a serum 25(OH)D threshold effect and the fact that it may require approximately 2-3 months of supplementation to reach a steady state.[21] There is some individual variation in what dose is required to reach a particular serum 25(OH)D, possibly due to a nonlinear serum response to dosing; vitamin D is metabolized more quickly at increased serum levels.[7] That said, most people eventually will raise their serum 25(OH)D by 10 ng/mL with supplementation of 1,000 IU,[22] and this amount of vitamin D supplementation is thought to bring 50% of people above a serum 25(OH)D level of 30 ng/mL.[23] None of the clinical trials in this review provide sufficiently convincing results relevant to dosing to expand upon the past recommendations focused more upon serum 25(OH)D.

Adverse Effects

The above-mentioned review of 13 trials reported adverse effects as "rare" and only two instances of hypercalcemia necessitating a reduction or discontinuation of vitamin D.[18] Other trials reported no adverse effects,[16] or no difference in the rate of adverse effects between vitamin D and placebo arms.[15] One oft-quoted editorial mentions the safety of vitamin D for people of all ages, except for those with granulomatous diseases who would need a lower dose.[22]

Conclusion

From the times of rampant rickets and tuberculosis to the present day, observational data have shown a close connection between low serum 25(OH)D and the incidence of URIs, which could partly explain the seasonality of many URI etiologic agents. Human clinical trials have illustrated a few themes. People with lower serum 25(OH)D are at risk for more severe respiratory disease, but also may be the people who respond better to vitamin D supplementation. It seems that a minimum serum 25(OH)D level of 30-35 ng/mL is necessary to provide a protective effect against URIs, depending on the study. Published clinical trials have used vitamin D doses between 400-2,000 IU daily, though in some cases supplementation began in the winter, apparently too late to provide benefit if steady state 25(OH)D requires 2-3 months of treatment.

Recommendation

Vitamin D is a therapy of minimal risk, but possibly significant benefit with respect to URIs; therefore, until proven otherwise and for a growing number of health effects, all clinicians should be recommending vitamin D supplementation unless specifically contraindicated. Conforming to the research results reviewed here, supplementation should begin during the fall season, well in advance of the winter URI "season." The exact dose to be used is still a matter of speculation, and researchers instead have focused on the serum 25(OH)D thought to be protective; practitioners should aim for levels of at least 30-35 ng/mL for their patients. ■

References

1. Chesney RW. Vitamin D and the magic mountain: The anti-infectious role of the vitamin. *J Pediatrics* 2010;156:698-703.
2. Hewison M. Vitamin D and the immune system: New perspectives on an old theme. *Endocrinol Metab Clin North Am* 2010;39:365-379.
3. Bartley J. Vitamin D, innate immunity and upper respiratory tract infection. *J Laryngol Otol* 2010;124:465-469.
4. Cannell JJ, et al. Epidemic influenza and vitamin D. *Epidem Infect* 2006;134:1129-1140.
5. White AN, et al. Let the sun shine in: Effects of ultraviolet radiation on invasive pneumococcal disease risk in Philadelphia. *BMC Infect Dis* 2009;9:196.
6. Lange NE, et al. Vitamin D, the immune system and asthma. *Expert Rev Clin Immunol* 2009;5:693-702.
7. Sabetta JR, et al. Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* 201014;5:e11088.
8. Ginde AA, et al. Association between serum 25-hydroxyvitamin D level and upper respiratory tract in the third National Health and Nutrition Examination Survey. *Arch Intern Med* 2009;169:384-390.
9. Aloia JF, et al. A randomized controlled trial of vitamin D3 supplementation in African American women. *Arch Intern Med* 2005;165:1618-1623.
10. Avenell A, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and postmenopausal osteoporosis. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD000227. DOI: 10.1002/14651858.CD000227.pub3.
11. Roth DE, et al. Vitamin D status is not associated with the risk of hospitalization for acute bronchiolitis in early childhood. *Eur J Clin Nutr* 2009;63:297-299.
12. McNally JD, et al. Vitamin D deficiency in young children with severe acute lower respiratory infection. *Pediatr Pulmonol* 2009;44:981-988.
13. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357:266-281.
14. Bouillon R, et al. Vitamin D and health: Perspectives from mice and man. *J Bone Min Res* 2008;23:974-979.
15. Li-Ng M, et al. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiol Infect* 2009;137:1396-1404.
16. Urashima M, et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A infection in schoolchildren. *Am J Clin Nutr* 2010;91:1255-1260.
17. Wejse C, et al. Vitamin D as supplementary treatment for tuberculosis: A double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2009;179:843-850.
18. Yamshchikov AV, et al. Vitamin D for treatment and prevention of infectious diseases: A systematic review of randomized controlled trials. *Endocr Pract* 2009; 15:438-449.
19. Laaksi I, et al. Vitamin D supplementation for the prevention of acute respiratory tract infection: A randomized, double-blinded trial among young Finnish men. *J Infect Dis* 2010;202:809-814.
20. Manaseki-Holland S, et al. Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: A randomised controlled trial. *Trop Med Int Health* 2010;15:1148-1155.
21. Vieth R, et al. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001;73:288-294.
22. Grant WB. Vitamin D supplementation could reduce the risk of type A influenza infection and subsequent pneumonia. *Pediatr Infect Dis J* 2010;29:987.
23. Bischoff-Ferrari HA, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;84:18-28.

Evening Primrose Oil for Symptoms of Premenstrual Syndrome and Menopause

By Dónal P. O'Mathúna, PhD

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A SHIFT HAS OCCURRED IN RECENT YEARS FROM VIEWING menopause as "a natural life event" experienced by women to "a condition that requires medical manage-

Summary Points

• Evening primrose oil is a popular complementary treatment for the symptoms of premenstrual and menopausal symptoms.

• Controlled clinical trials consistently demonstrate that evening primrose oil is no better than placebo in treating such symptoms.

• The oil is a rich source of gamma-linolenic acid (GLA), which is useful for general health.

ment."[1] Following concerns about adverse events with hormone replacement therapy (HRT), many women have turned to complementary and alternative medicine (CAM), including herbs and dietary supplements. A survey in 2009 found that 45% of women who had discontinued HRT continued to use CAM, with evening primrose oil being one of the more common interventions used.[1] Another survey found that 80% of women suffering from symptoms of premenstrual syndrome (PMS) use over-the-counter products, including herbs and natural remedies.[2] Given that surveys report that up to 75% of women experience some PMS symptoms, clinicians should be aware of the evidence regarding this popular herbal remedy so they can provide patients with reliable information.[3]

Background

Evening primrose oil is obtained from the seeds of the yellow primrose (*Oenothera biennis*), a North American wildflower.[4] Early English settlers brought the flower back to England where it was cultivated for its nut-flavored root. An oil was extracted from the seeds and became known as the King's Cure-All. Surveys have found that it remains very commonly used in England. Two evening primrose oil products were licensed by Britain's Medicines Control Agency. The products were available by prescription to treat atopic eczema and mastalgia (breast pain). However, in 2002 the licenses were revoked after a review of studies on its effectiveness found insufficient evidence to continue its official approval.[5]

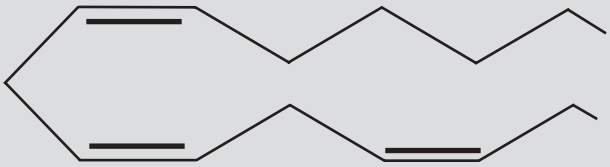
Evening primrose oil contains a high proportion of essential fatty acids. The two most common types present in the oil are linoleic acid (about 65%) and gamma-linolenic acid (GLA, 8-10%), both omega-6 fatty acids.[6] The oil also contains alpha-linolenic acid, an omega-3 fatty acid.[7] Evening primrose oil is valued primarily for its GLA, being one of the richest plant sources. Only borage oil (24%) and black currant seed oil (16%) contain more GLA (*see box*). Unlike most omega-6 fatty acids, GLA is converted into a number of anti-inflammatory prostaglandins in the body, which is why evening primrose oil is often recommended to treat numerous chronic inflammatory diseases.

Mechanism of Action

How evening primrose oil might relieve premenstrual or menopausal symptoms is not clear. Some studies have shown that women with premenstrual syndrome tend to have lower than normal levels of GLA.[6] Epidemiological studies have shown a connection between low dietary levels of GLA and a number of illnesses. However, a precise mechanism of action for evening primrose oil is not known.

Gamma-linolenic acid

Gamma-linolenic acid (GLA) is an n-6 (omega-6) poly-unsaturated fatty acid. It is composed of 18 carbon atoms and three double bonds. The chemical structure of GLA is:



Gamma-linolenic acid

GLA is found naturally to varying extents in the fatty acid fraction of some plant seed oils. In evening primrose seed oil, it is present in concentrations of 7-14% of total fatty acids; in borage seed oil, 20-27%; and in black currant seed oil, 15-20%. GLA also is found in some fungal sources. GLA is produced naturally in the body as the metabolite of the essential fatty acid linoleic acid. Under certain conditions, GLA may become a conditionally essential fatty acid. GLA is present naturally in the form of triacylglycerols. The stereospecificity of GLA varies among different oil sources.

GLA, supplied in the form of evening primrose oil or borage seed oil, has been studied for many years for its possible effects in arthritis and other inflammatory processes. It has been shown to suppress inflammation and reduce joint tissue injury in many animal models.

Adapted from: Evening Primrose. Herbals & Supplements. Available at www.pdrhealth.com/drugs/altmed/altmed-a-z.aspx?letter=E. Accessed Nov. 10, 2010.

Clinical Studies

Very few high-quality studies have been conducted using evening primrose oil for specific conditions in humans. A 1994 study remains the only controlled study of evening primrose oil for menopausal symptoms.[8] The impact of evening primrose oil on hot flashes and night sweats was examined in 56 menopausal women randomized to either evening primrose oil (4 g/d plus 80 mg/d vitamin E) or placebo.[9] Only 35 women finished the 6-month study. Although all women showed some improvements, no significant differences were found between the two groups.

Evening primrose oil has been one of the more popular natural therapies for PMS. Four randomized controlled trials have been identified on this topic,[3,10] all conducted in the 1980s and 1990s. Three of the four were double-blinded, but all had small sample sizes (ranging from 22 to 38). The women took between 3 and 6 g evening primrose oil daily for between 4 and 10 months. All four studies failed to show any significant difference in overall PMS symptoms between evening primrose oil and placebo. One of the studies found that depression scores were significantly lower in the evening primrose oil group than the placebo group ($P < 0.05$).[11] However, this was also the one study that was not double-blinded. This is an important limitation as other studies have found up to 80% of women report improved PMS symptoms with placebo.[12]

Evening primrose oil has been used to treat mastalgia, including that associated with PMS. One of the largest studies ever conducted on mastalgia randomized 555 women to one of four groups.[5] Each woman took 4 g/d of capsules containing either evening primrose oil alone, evening primrose oil plus multivitamins, multivitamins alone, or placebo. After 4 months of blinded treatment, all groups showed an average 35% reduction in breast pain. No statistically significant differences were found between any of the four groups. The study continued as an open trial for another 6 months with all subjects receiving evening primrose oil, either with or without multivitamins. Breast pain was reduced by another 50%, but with no differences between the two groups. The researchers concluded that evening primrose oil was not superior to placebo in treating mastalgia. A meta-analysis of randomized controlled trials for mastalgia concluded that while bromocryptine, danazol, and tamoxifen use resulted in significant pain relief, evening primrose oil did not.[13] This conclusion was based on the results of four controlled trials.

Adverse Effects

The most commonly reported adverse effects associated with evening primrose oil in clinical trials are difficulties swallowing the large capsules and gastrointestinal complaints. Most studies have used four 500 mg capsules taken twice daily, with up to 6 g/d used. The gastrointestinal symptoms are usually mild to moderate, with nausea being the most common. The effects of long-term use have not been examined. The withdrawal of evening primrose oil's license in Britain was not based on concerns about safety, but due to a lack of evidence of effectiveness.

As a side note, evening primrose oil has been popularly recommended to shorten the duration of labor, but a retrospective study found that women taking the oil during their pregnancies were in labor for an average of 3 hours longer.[14] Although causation could not be established, women who are pregnant or breast feeding should, in general, avoid herbs and dietary supplements until they have been demonstrated to be safe.

Conclusion

A relatively small number of studies have examined the effectiveness of evening primrose oil in treating PMS and menopausal symptoms. The controlled studies consistently show that evening primrose oil is no more effective than placebo. Since these symptoms are known to respond well to the placebo effect, and to vary in random and cyclical ways, this may explain why the use of evening primrose oil remains popular.

In spite of its popularity, evening primrose oil is no more beneficial than placebo in treating menopausal or PMS symptoms. Some women may have very low levels of GLA in their diet, or may not produce adequate amounts within their bodies. They may receive some general health benefits from supplementing their diet with evening primrose oil. However, its usefulness in treating any particular condition associated with premenstrual syndrome or menopause is not supported by clinical research. ■

References

1. Kupferer EM, et al. Complementary and alternative medicine use for vasomotor symptoms among women who have discontinued hormone therapy. *J Obstet Gynecol Neonatal Nurs* 2009;38:50-59.
2. Domoney CL, Vashisht A, Studd WW. Premenstrual syndrome and the use of alternative therapies. *Ann NY Acad Sci* 2003;997:330-340.
3. Whelan AM, Jurgens TM, Naylor H. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: A systematic review. *Can J Clin Pharmacol* 2009;16:e407-e429.
4. Haimov-Kochman R, Hochner-Celnikier D. Hot flashes revisited: Pharmacological and herbal options for hot flashes management. What does the evidence tell us? *Acta Obstet Gynecol Scand* 2005;84:972-979.
5. Goyal A, Mansel RE; Efamast Study Group. A randomized multicenter study of gamolenic acid (Efamast) with

and without antioxidant vitamins and minerals in the management of mastalgia. *Breast J* 2005;11:41-47.

6. Hardy ML. Herbs of special interest to women. *J Am Pharm Assoc (Wash)* 2000;40:234-242.
7. Philp HA. Hot flashes—A review of the literature on alternative and complementary treatment approaches. *Altern Med Rev* 2003;8:284-302.
8. Carroll DG. Nonhormonal therapies for hot flashes in menopause. *Am Fam Physician* 2006;73:457-464.
9. Chenoy R, et al. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994;308:501-503.
10. Stevinson C, Ernst E. Complementary/alternative therapies for premenstrual syndrome: A systematic review of randomized controlled trials. *Am J Obstet Gynecol* 2001;185:227-235.
11. Puolakka J, et al. Biochemical and clinical effect of treating the premenstrual syndrome with prostaglandin synthesis precursors. *J Repro Med* 1985;30:149-153.
12. Khoo SK, et al. Evening primrose oil and treatment of premenstrual syndrome. *Med J Aust* 1990;153:189-192.
13. Srivastava A, et al. Evidence-based management of mastalgia: A meta-analysis of randomised trials. *Breast* 2007;16:503-512.
14. Dove D, Johnson P. Oral evening primrose oil: Its effect on length of pregnancy and selected intrapartum outcomes in low-risk nulliparous women. *J Nurse Midwifery* 1999;44:320-324.

Insult Becoming Injury—Stress and Metastases

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *A murine model was employed to assess the effects of chronic stress on metastatic breast cancer spread. The researchers used a variety of tools to investigate the neuroendocrine, molecular, and cellular effects of chronic stress in this setting. Their findings suggest that chronic stress induces a significant increase in the extent of cancer spread through the activity of the sympathetic nervous system. The findings open numerous research questions yet to be answered, as well as great therapeutic possibilities.*

Source: Sloan EK, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res* 2010;70:7042-7052.

The impact of chronic psychosocial stress on immune system function has been the focus of many studies, the results of which largely suggest an associated impairment of various immune compartments. Fewer studies have been performed that specifically address the impact of stress on immune activity and cancer. The data regarding an association between stress and the initial development of breast cancer, for example, are inconsistent, while other studies have specifically linked an increased spread of cancer to stress. The authors of this animal study looked at the effect of chronic stress on the distant metastatic spread of primary breast cancer.

Six-week old female mice, some with an intact immune system and others bred to be T cell deficient, were injected with 66c14 mammary adenocarcinoma cells into the 4th mammary fat pad for spontaneous metastasis studies, or into the tail vein for organ colonization studies. The frequency and quantity of metastases were tracked in live mice through repeated use of a non-invasive optical imaging process that can resolve as few as 3,000 cells. In addition, mice under anesthesia were photographed and metastases measured by triplicate determination of bioluminescence in a region distant from the primary tumor (primarily the chest region and focusing on the lung, and axillary and brachial lymph nodes). Tissue-specific metastases were measured ex vivo by bioluminescence immediately after sacrifice on day 28, or by microscopic evaluation on day 41 in experiments involving prior removal of the primary tumor.

Mice were randomly assigned to home cage control conditions or to 2 hours of restraint per day for 20 days that began 5 days before tumor cell inoculation, or for a period of 14 days beginning 2 days after surgical removal of the primary tumor. Restraint consisted of being placed in a confined space that prevented the mice from moving freely, but that did not press on them or induce physical injury or pain. This method has reportedly been shown to induce a state of chronic stress as demonstrated by neuroendocrine activation (increases in circulating catecholaminergic neurotransmitters and corticosterone levels), weight loss, and anxiety-like behaviors.

Mice received isoproterenol at a receptor-saturating dose by daily s.c. injection commencing 5 days before tumor inoculation to study the effects of beta-adrenergic agonism. For beta-adrenergic antagonist studies, two days before commencing stress or control conditions mice were implanted with a 21-day release pellet containing either propranolol, in a dose sufficient to block peripheral beta-adrenergic receptors, or placebo. Additional studies included determination of cAMP synthesis, analysis of macrophage infiltration and vascular density, and expression of metastasis-related genes.

Results showed metastatic spread of disease in both

the stressed and control mice. Noninvasive imaging in control mice revealed a progressive increase in the spread of tumor cells to lung and chest lymph nodes that plateaued 21 days after tumor cell inoculation; however, chronic stress increased the metastatic spread of primary breast tumor cells to distant tissues 38-fold vs. controls ($P = 0.04$). Stress increased metastasis in the lung 37-fold ($P = 0.034$) and 67% in the chest lymph nodes ($P = 0.009$). Increases occurred in both the number and size of metastatic masses. Notably, primary tumor growth rate was not impacted significantly by stress, but there was an associated increase in the expression of proinflammatory and prometastatic genes within the primary tumor.

When tumor cells were injected directly into the bloodstream and bioluminescent assays of distant tissue tumor signals were performed, a 3.3-fold increase in distant colonization rates as a function of stress was found. Ex vivo analyses of tissue harvested 27 days after injection found that chronic stress increased lung tumor colonization 2.5-fold ($P = 0.038$) and lymph node colonization 2.1-fold ($P = 0.037$). In another experiment, restraint was initiated only after surgical removal of the primary tumor to examine the effects of stress on metastases independent of effects on the primary tumor. Results showed that stress increased metastatic spread 2.7-fold ($P = 0.05$).

When unstressed mice were administered the beta-agonist isoproterenol, metastatic spread to distant tissues increased 22-fold compared with saline-treated controls ($P = 0.03$). Treatment with the beta-blocker propranolol had no significant effect on metastatic burden in control mice ($P = 0.08$); however, propranolol completely blocked stress-induced metastatic spread in the mice subjected to chronic restraint ($P < 0.0001$). Propranolol had no effect on primary tumor growth in the mammary fat pad in either group. Additional investigation showed that T cells were not associated with the immune impact of chronic stress, but that there was a stress-induced recruitment of immune cells, specifically macrophages, that was blocked with administration of propranolol.

The study authors state their findings identify sympathetic nervous system activity as playing an important role as a physiologic regulator of breast cancer metastasis to lymph nodes and lung in both immunocompetent and T cell deficient mice through beta-adrenergic signaling. As a downstream result, activated macrophages are recruited to the primary tumor site and there is an increase in prometastatic gene expression.

■ COMMENTARY

It is puzzling that research showing how chronic stress can mediate the risk of metastatic breast cancer spread has not found a wider audience in the lay press. This should be big news, and promising news, coming out of a well-done study protocol. Yes, these are animal data, but they help solidify a hypothesis in humans where exploration has already begun.

Conventional medical studies have suggested that employing beta-blockade might lessen the risk for metastases in the setting of cancer. CAM, and some conventional, trials have highlighted findings suggesting a myriad of benefits from stress management in the setting of cancer, but few if any have explored the neuroendocrine impacts of psychosocial tension.

Stress induces the release of norepinephrine into both the local microenvironment and systemic circulation. As the authors note, nerve fibers from the sympathetic nervous system are present in organs that serve as prime targets for breast cancer metastasis, including lymph nodes, lung, and bone. The new findings suggest that the effects of the autonomic nervous system extend even to poorly innervated structures, including solid tumors.

This article raises many questions, starting with a significant ethical one—should animals be subjected to this type of treatment in the name of human medical science? *Alternative Medicine Alert* is not the proper forum for this discussion, but one would be hard-pressed to read this study and not come away with the question.

On the other hand, there are findings from this study that have real and actionable impact, at least in the form of generating new research questions such as: should all women with breast cancer be placed on low-dose beta-blocker therapy? Can beta-blocker therapy be of benefit in other forms of cancer treatment? Would stress management techniques such as meditation, exercise, and massage therapy have benefit with respect to limiting the spread of metastatic disease by quelling the degree of neuroendocrine activation in an inherently stressful situation like the diagnosis of cancer? Is there reason to combine beta-blocker therapy and specific stress management therapy for people with breast cancer? If stress management techniques are of benefit in this manner, are they all of equivalent effectiveness?

These findings are truly exciting—they bring hope to all who are touched by cancer; they raise new prospects for ways that people might lessen their risk for metastatic spread of cancer simply by improving lifestyle habits (stress management); and they point out that select CAM therapies have hard conventional bench data supporting their potential clinical use. We await human data that parallels this study's findings, but how good to be able to tell our patients that engaging in stress management practices upon receiving a diagnosis of breast cancer, if not other tumors, may not only help them feel better but might also help limit spread of the disease. ■

A Whole New Headache—Acetaminophen and Coronary Artery Disease

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *It has long been assumed that acetaminophen, the common analgesic agent, is relatively safe for people with known coronary artery disease, in contrast to NSAIDs and COX-2 inhibitors. But assumptions can be dangerous, and this small study suggests that acetaminophen use may have similar risks associated with it, specifically increases in blood pressure.*

Source: Sudano I, et al. Acetaminophen increases blood pressure in patients with coronary artery disease. *Circulation* 2010;122:1789-1796.

Concerns about adverse cardiovascular effects with the use of either non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX-2) inhibitors in people with known coronary artery disease (CAD) often lead to recommendations to take acetaminophen (Tylenol) for the management of chronic pain. Acetaminophen is a weak analgesic, but has been considered a safer alternative to NSAIDs and COX-2 inhibitors in this setting. At least, that was the assumption.

The authors of this Swiss prospective, randomized, double-blind, placebo-controlled, crossover study sought to investigate the safety of acetaminophen in patients with stable CAD, focusing primarily on ambulatory blood pressure (ABP) readings, and endothelium-dependent and -independent vasodilation. People with known CAD on stable cardiovascular medications for at least the prior month were recruited from a cardiology specialty clinic in Zurich (exclusion criteria included left ventricular ejection fraction < 50%, chronic pain, and use of other analgesics).

Subjects were randomized to receive either 1 g acetaminophen (containing essentially no measurable sodium) three times daily or matching placebo for 2 weeks. There followed a washout period of 2 weeks, and then subjects were crossed over into the other treatment grouping. At baseline, 2, 4, and 6 weeks, endothelial function was measured, blood and urine were collected, and clinical status assessed, all before the subjects took their usual morning drug therapy. Regular medications and study drug were then taken and 24-hour ABP monitoring commenced (measurements were taken every 15 minutes during the day, every 30 minutes at night). Secondary measures of interest included platelet function, endothelial progenitor cells, and markers of inflammation and oxidative stress, among others.

Following analysis of data from 22 subjects, it was determined that a larger sample size was necessary for adequate statistical power. A total of 37 subjects were enrolled with final data available on 33 (4 subjects withdrew, reportedly for personal reasons, after their first visit).

Ingestion of acetaminophen 1 g TID for 2 weeks' time resulted in a significant increase in systolic blood pressure from 122.4 to 125.3 mm Hg (P = 0.021) and diastolic blood pressure from 73.2 to 75.4 mm Hg (P = 0.024) compared with placebo. Heart rate also increased while subjects were on acetaminophen, from 68.2 to 70.8 bpm, but not while on placebo, although the difference did meet statistical significance. No other differences between the treatment and placebo phase of the crossover trial were identified, including for flow mediated dilation. One subject experienced a significant increase in gamma-glutamyltransferase during the acetaminophen phase that normalized after cessation of treatment (subject denied alcohol use).

The researchers concluded that acetaminophen administration in the setting of known CAD results in a significant increase in both systolic and diastolic blood pressures, thus representing a potential public health concern.

■ COMMENTARY

It is well established that selective and non-selective NSAIDs are associated with an increased risk of cardiovascular events, thus the current guidelines recommending avoidance of NSAIDs and COX-2 inhibitors in people with established CAD or who are at high cardiovascular risk for disease and a preference for acetaminophen. This is the first study to question the assumption of the cardiovascular safety of acetaminophen, and the findings are troubling. The observed increase in blood pressure noted with short-term use of acetaminophen was within the range of hypertensive effects seen with some traditional NSAIDs, and it is accepted that an incremental risk of cardiovascular and cerebrovascular disease exists with increasing blood pressure levels.

The authors note that acetaminophen (Tylenol) is one of the most commonly used drugs worldwide, often as a major ingredient in cold and flu medication, and that sporadic studies have linked acetaminophen with raised blood pressure or an increased risk of cardiovascular disease. Inhibition of prostaglandin synthesis is induced with NSAID use, but acetaminophen is considered to have weak activity in this regard. The authors speculate on there being a central mechanism at work due to the presence of increases in both blood pressure and pulse with acetaminophen.

A small sample size was employed because patients in the study did not present with pain, and a crossover design was used to limit the number of patients exposed to a drug from which they would likely not benefit. Future studies will certainly need to be designed carefully, as the ethical considerations of randomizing subjects in pain to active vs. placebo agents are substantial.

A significant proportion of people with CVD also experience chronic pain, which in light of this study begs the question, what types of analgesia should practitioners be recommending to patients with CVD? The answer is not yet clear. Acupuncture is an effective means of relieving some forms of chronic pain and there are suggestions in the medical literature that it may help lower blood pressure, but not everyone has access to or can afford acupuncture. Natural anti-inflammatory agents, such as turmeric, boswellia and ginger, may be beneficial but the same concerns about blood pressure need to be investigated.

Acetaminophen still may end up being considered a reasonable option for some cardiac patients with chronic pain—the trial lasted only 2 weeks and the adverse effects may have plateaued and dropped with more time. However, they also may have worsened with a longer duration of administration. In addition, concerns about liver toxicity with inappropriate acetaminophen use have been growing. We await further studies to help direct our clinical recommendations. Assumptions, it is clear, can be problematic whether they originate in conventional or in CAM therapeutics, and nothing can, or should, be taken for granted when it comes to optimizing health. ■

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Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

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

49. Which of the following is true regarding the use of vitamin D supplementation to prevent or treat URIs?

a. Serum 25(OH)D is less important than the vitamin D dose used to prevent/treat URIs.

b. There is convincing data that vitamin D can decrease the incidence of URIs in adults even if they already have adequate serum 25(OH)D.

c. With respect to pediatric ICU admissions for lower respiratory tract infections, researchers aren't sure about the role of supplementation but low 25(OH)D definitely correlates with increase admission rates.

d. After supplementation begins, steady state 25(OH)D occurs in 2-3 weeks, so this is a relatively fast-acting intervention.

50. How long does it take for patients to reach a steady state of vitamin D after beginning supplementation?

a. 2-3 weeks

b. 2-3 months

c. 6 months or more

51. Gamma-linolenic acid (GLA) contained in evening primrose oil belongs to the group of:

a. saturated fatty acids.

b. omega-6 fatty acids.

c. omega-3 fatty acids.

d. None of the above

52. The evidence from randomized controlled trials is that evening primrose oil is:

a. more effective than placebo for relieving PMS symptoms.

b. more effective than placebo for relieving menopausal symptoms.

c. no more effective than placebo for relieving PMS symptoms.

d. None of the above

53. The principal adverse effect from taking evening primrose oil is:

a. gastrointestinal problems.

b. headache and dizziness.

c. leg cramps.

d. menopause.

54. :Researchers in a recent study concluded that acetaminophen administration in the setting of known coronary artery disease results in a significant increase in both systolic and diastolic blood pressures, and thus represents a potential public health concern.

a. True

b. False

Answers: 49. c, 50. b, 51. b, 52. c, 53. a, 54. a.

In Future Issues:

Acupuncture and Hot Flushes

Glucosamine for Osteoarthritis

Proton Pump Inhibitor Therapy and Increased Risk of Respiratory Infections

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Tiotropium for Uncontrolled Asthma

In this issue: Tiotropium for uncontrolled asthma, sibutramine pulled from market, incidence and mortality data from WHI, FDA Actions.

Tiotropium for uncontrolled asthma

Tiotropium, a long-acting anticholinergic inhaler, is approved for treatment of chronic obstructive pulmonary disease. A new study suggests that it may also be effective for patients with asthma.

In a study of 210 adults with asthma with inadequate control with inhaled glucocorticoids, tiotropium was compared to doubling the dose of glucocorticoids, and was also compared to the addition of salmeterol, a long-acting beta agonist (LABA). Tiotropium was superior to doubling the dose of inhaled glucocorticoid as assessed by measuring the morning peak expiratory flow (PEF) ($P < 0.001$). It also improved evening PEF, asthma control days, and FEV1, as well as daily symptom scores. The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and was superior to salmeterol in measures of prebronchodilator FEV1 ($P = 0.003$).

The authors conclude that tiotropium is superior to doubling the dose of glucocorticoid in patients with inadequately controlled asthma, and is equivalent to the addition of salmeterol in the same patient group (published online *N Engl J Med* Sept. 19, 2010). This study is important because it may result in options for patients with poorly controlled asthma beyond adding a LABA. Recently, asthma experts and the FDA have questioned the safety of LABA therapy (FDA Drug Safety Communication June 2, 2010), and a recent meta-analysis suggests that use of LABAs without concomitant inhaled corticosteroids increase the risk for intubation or death (*Am J Med* 2010;123:322-328). ■

Sibutramine pulled from market

Abbott Laboratories announced in October that it is withdrawing the weight-loss drug sibutramine (Meridia®) from the market. The move comes a month after the FDA finished a review of the drug and found that patients with cardiovascular disease or diabetes given sibutramine had a significantly higher rate of serious cardiovascular events compared to placebo. The drug was originally approved in 1997. In a news release, the FDA states "physicians are advised to stop prescribing Meridia to their patients and patients should stop taking this medication." *The Wall Street Journal* reports that while Meridia may be off the market, sibutramine is still available illegally in many weight-loss nutritional supplements, most of which are available via the Internet from oversee suppliers. The supplements are marketed as "all-natural" and their labels list only herbal ingredients. The FDA recently advised consumers that Slimming Beauty Bitter Orange Slimming Capsules contains sibutramine, and last year published a list of more than 50 other supplements containing the banned drug. For complete list of supplements containing sibutramine go to: www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm136187.htm. ■

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Dr. Elliott reports no financial relationships to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Incidence and mortality data from WHI

In 2002, the Women's Health Initiative (WHI) study was stopped early after 5.6 years when data showed that combination estrogen and progesterone therapy increased the risk of breast cancer. Mortality data had never been reported from WHI, however, and other studies have suggested that hormone therapy-associated breast cancers might have a more favorable prognosis than other breast cancers. A new analysis of WHI data dispels that notion.

The current study is a follow-up study of more than 16,000 women enrolled in WHI who were randomized to conjugated equine estrogen 0.65 mg per day plus medroxyprogesterone 2.5 mg per day (Prempro®) or placebo. Participants were followed for an average of 11 years with the main outcome measure being breast cancer incidence and breast cancer mortality. Women on hormone therapy had a higher rate of breast cancer compared to women on placebo (0.42% vs 0.34% per year; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; $P = 0.004$) and breast cancers in the hormone group were more likely to be node-positive (23.7% vs 16.2%; HR, 1.78; 95% CI, 1.23-2.58; $P = 0.03$). The death rate associated with breast cancer was higher in the hormone group (0.03% vs 0.01% per year; HR, 1.96; 95% CI, 1.00-4.04; $P = 0.049$), a finding that barely reached statistical significance because of the low number of cancers in either group.

The authors conclude that estrogen plus progesterone was associated with a higher breast cancer incidence, as well as cancers that were more commonly node-positive. Breast cancer mortality was also higher in the combined hormone group (*JAMA* 2010;304:1684-1692). An accompanying editorial points out that despite the borderline statistical significance of these findings it is likely that "the increase in breast cancer deaths due to hormone therapy has been underestimated in the current study." However, it is still unclear whether short courses of hormone therapy for relief of postmenopausal symptoms right after menopause may be safe and further research is needed "to determine whether lower doses or shorter durations of hormone therapy could alleviate menopausal symptoms without increasing cancer risk" (*JAMA* 2010;304:1719-1720). ■

FDA actions

The FDA has approved fingolimod, the first oral drug for the treatment of relapsing forms of multiple sclerosis. Fingolimod is a sphingosine 1-phosphate receptor modulator that is believed to reduce migration of lymphocytes into the central nervous system. Compared to interferon beta-1a, the annualized relapse rate was significantly lower with fingolimod. Patients need to be monitored for decreased heart rate and elevation of liver transaminases. Fingolimod is given as a once-daily 0.5 mg tablet. It is marketed by Novartis as Gilenya™.

As anticipated, the **FDA has approved dabigatran to prevent strokes and blood clots in patients with atrial fibrillation.** The drug is a direct thrombin inhibitor and is given orally twice a day. The approval was based on the RE-LY trial, which showed that dabigatran at 150 mg given twice a day was superior to warfarin for this indication. Unlike warfarin, dabigatran requires no monitoring. Dabigatran will be available in 75 mg and 150 mg capsules and will be marketed as Pradaxa® by Boehringer Ingelheim Pharmaceuticals.

The FDA has ordered a labeling change for bisphosphonates, warning of the risk of atypical femoral fractures. In March, the FDA announced an ongoing safety review of bisphosphonates and the occurrence of subtrochanteric and diaphyseal femoral fractures. The new warning is a result of that review and, while not acknowledging a direct link, the warning suggests that these fractures may be related to use of bisphosphonates for longer than 5 years. The agency further suggests that health care professionals consider periodic reevaluation of the need for continued bisphosphonate therapy in patients who have been on the drugs for more than 5 years. The labeling change will only affect bisphosphonates approved for osteoporosis, which include alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), and zoledronic acid (Reclast®).

The FDA has approved extended-release naltrexone to treat and prevent relapse of patients with opioid dependence who have undergone detoxification treatment. Extended-release naltrexone is administered by intramuscular injection once a month, and blocks opioid receptors in the brain. It was initially approved in 2006 to treat alcohol dependence. The drug is only approved for patients who have completed rehabilitation, otherwise it may trigger opioid withdrawal. The efficacy of naltrexone was shown in a 6-month placebo-controlled trial in which treated patients were more likely to stay in treatment and refrain from using illicit drugs. Extended-release naltrexone injection is marketed as Vivitrol® by Alkermes Inc. ■

ALTERNATIVE MEDICINE ALERT™

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