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Vitamin D Supplementation Dosage: A Road Map through the Confusion

By David Kiefer, MD

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RESEARCHERS AND CLINICIANS NOW RECOGNIZE VITAMIN D AS BEING A nutrient extremely important for human health. It has connections to many different body systems, with support from clinical trials and basic science research. There is evidence of efficacy for its therapeutic use in several medical conditions, as well as of the dangers associated with vitamin D insufficiency or deficiency.

What is less clear are the exact doses necessary to maintain vitamin D "health" or repair inadequacies, and what the evidence is upon which these official and anecdotal recommendations are made. Communication with colleagues recently illustrated the range of doses being used; I have heard about 1,000-2,000 IU daily for maintenance, up to 5,000 IU daily or 50,000 IU weekly for repletion, or 100,000 IU daily for three days during acute respiratory illness.

This review will draw upon a variety of sources to address this issue and provide specific clinically relevant dosing suggestions, applicable to a variety of patient situations.

Forms

Before launching into a description of the medical research, it is important to get a handle on vitamin D terminology. A variety of vitamin D forms and dosing schedules have been used in clinical trials *(see Table 1)*. Most commonly used in supplementation are ergocalciferol (vitamin D2), a yeast-based derivative, or cholecalciferol (vitamin D3); there are some data pointing out that vitamin D2 is approximately 30% less effective in improving serum vitamin D levels than vitamin D3.[1-3] Some researchers have studied the use of "active" forms of vitamin D, or the two forms, 1-alpha-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3, that have already been partially or fully metabolized, respectively. These "active" forms

Table 1. Vitamin D terminology

Term (alphabetical)	Description
Alfacalcidol (1-alpha-hydroxyvitamin D3)	One hydroxyl group added via renal activation to vitamin D3
Calcidiol (25-hydroxyvitamin D)	The form most commonly tested for in blood/serum
Calcitriol (1,25-dihydroxyvitamin D3)	Two hydroxyl groups added to vitamin D3 via liver and renal activation; Considered the most physiologically active
Cholecalciferol (vitamin D3)	Manufactured by the ultraviolet irradiation of the 7-dehydrocholesterol in lanolin
Ergocalciferol (vitamin D2)	Manufactured by the ultraviolet irradiation of the ergosterol in yeast; A prescription form of this is available

have been studied in clinical trials, finding no difference in fall prevention when compared to ergocalciferol or cholecalciferol, but an increased rate of side effects such as hypercalcemia.[4]

Of note, most dosing is in terms of International Units, or IU (1 IU is the equivalent of 25 ng of vitamin D).

General Dosing Guidelines

Recommendations for vitamin D supplementation are varied and dependent on many factors. The top of the vitamin D treatment algorithm is to decide whether administration is for the treatment of vitamin D deficiency or insufficiency, or simply to maintain adequate vitamin D levels. For the former, recommendations vary, mostly because there is still some controversy about target serum 25-hydroxyvitamin D levels. Other considerations are oral vs. intramuscular dosing (seemingly equivalent[3]), and intermittent vs. daily dosing (still unresolved,[5] but considered equal daily vs. weekly vs. monthly[6]). Of note, supplementation with 1,000 IU daily is thought to increase serum 25(OH)D by 10 ng/mL.[6]

Dosing from Expert Panels and Governmental Groups

As a baseline, the Dietary Reference Intake from the Institute of Medicine ranges from 200 IU to 600 IU, depending on age; these 1999 recommendations are in the midst of being re-evaluated with a report due in September 2010.[1,7] Most experts now feel that, especially in the absence of regular sun exposure or for people with darker skin, maintenance dosing should be 800-1000 IU;[8] certain populations may require even higher dosages *(see below)*.

Dosing Guidance from Clinical Trials

There have been dozens of clinical trials testing the effects of supplementation of vitamin D, often with calcium, on various medical conditions. Another group of studies have attempted to correlate serum 25-hydroxyvitamin D levels with the absence or presence of clinical pathology; such research is relevant to vitamin D dosing insofar as the resulting changes in serum levels with particular dosages. A summary list of dosing employed and results from meta-analyses and review articles can be found in Table 1.

Delving into the particulars in two often-quoted meta-analyses lends some interesting insight to this topic. Recent Cochrane reviews on pain[9] and fractures[10] have addressed the effects of vitamin D supplementation. For chronic pain, the primary outcome reviewed, only one of four clinical trials found an effect of vitamin D supplementation; that trial used 1-2 μg of alfacalcidol daily over 16 weeks in rheumatoid arthritis. One of the other trials

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Table 2. Dosing extrapolated from clinical trials and meta-analyses

Clinical condition	Effective dose	Ineffective dose	Comments
Cardiovascular events[11]	N/A	1,000 IU/d or 100,000 IU every 4 months	Slight, non-statistically significant reduction
Chronic pain[9]	1-2 μg/d alfacalcidol or 100,000 IU/d calciferol	35 μg/d 25-hydroxy-vitamin D, or 50,000 IU D2 weekly	
Fall prevention[4]	700-1,000 IU/d	< 700 IU daily	Form varied in the individual trials: D3 perhaps slightly more effective; A serum 25(OH)D > 60 nmol/L needed for fall prevention
Fractures[10]	400-800 IU D3 + 1,000 mg calcium daily prevents hip fractures. Higher D3 doses might be more effective; Data most convincing for institutionalized elderly	Bolus or daily D2 or D3 equivalent to 830-1,000 IU/d	Alfacalcidol and calcitriol may also prevent fractures; Some concern over hypercalcemia with calcitriol use
Fractures[5]	400 IU/d vitamin D, when combined with calcium, reduces hip fractures and total fractures	10-20 μg (400-800 IU)/d	Calcium and vitamin D may also prevent vertebral fractures
Hypertension[12]	200-2,900 IU/d (one study used UVB light instead of supplemental vitamin D)		3 mmHg fall in systolic blood pressure; D2 and D3 more effective than "active" forms

had another positive effect: 100,000 IU daily of calciferol over 12 months for rheumatoid arthritis led to decreased anti-inflammatory medicine use compared to the placebo group. Two other trials, 35 μg per day (25 days of the month) of 25-hydroxyvitamin D over 9 months for polymyalgia rheumatica, and 50,000 IU D2 weekly over 3 months for diffuse musculoskeletal pain, showed no difference in subjective pain reports and visual analogue scale, respectively. For fractures, the Cochrane review of 45 trials (total participants 84,585) examined the use of several forms of vitamin D, with and without calcium, to prevent fractures in older people. The meta-analysis was able to comment on dosing, form, and connection with decreased fractures *(see Table 2 for details)*.

Other meta-analyses have examined the connection of vitamin D to other medical conditions; these are summarized in Table 2.[4,5,9-12]

Dosing from Experts and Review Articles

One excellent review outlines in detail a variety of approaches to maintenance dosing and correction of vitamin D insufficiency/deficiency, with nuances relevant to specific populations.[1] For example, 50,000 IU vitamin D2 every 2-4 weeks, or 800-1,000 IU D3 daily (except if pregnant or lactating, then use 1,000-2,000 IU D3 daily) are adequate maintenance doses, whereas 50,000 IU vitamin D2 every week for 8 weeks, then every 2-4 weeks, is one approach that can be used to correct deficiency.[1] Effective alternative maintenance dosages are 3,000 IU D2 daily or 100,000 IU D3 every 3 months.[1]

Dosing for Specific Populations

Children who are breastfeeding, especially if the mother is vitamin D-deficient, need vitamin D supplementation of 400 IU D3 daily up to age 1 year, and 400-1,000 IU daily from years 1-18.[1,13] Patients with kidney disease need annual monitoring of vitamin D status with dosing regimens that may include active vitamin D forms (both oral and IV), especially for stages 4 and 5 kidney failure.[1] For people suffering from malabsorption syndromes, 50,000 IU D2 is used orally daily to weekly, or adequate sun exposure; tanning beds have also been explored for use in this context;[1,6] it is possible that people who are obese also need higher vitamin D dosing.[1,6]

One specific group may be more susceptible to overtreatment with supplemental vitamin D. People with granulomatous disorders and some lymphomas may be more likely to develop hypercalcemia and hyperphosphatemia when

serum 25(OH)D levels rise above 30 ng/mL; supplementation with 400 IU D3 daily may be adequate to maintain vitamin D status and avoid adverse effects in this population.[1]

Vitamin D Dosing in the Context of Recommendations for Sun Exposure

The issue of sun exposure is relevant not only for people with problems absorbing or converting vitamin D; the medical literature contains many references to the relevance of sufficient sun exposure, for all ages, to vitamin D status and various disease states, of course balanced by concerns from the dermatological camp about increased risk of skin cancer. Approximately 10,000-25,000 IU of vitamin D can be generated by 10-15 minutes of direct whole-body sun exposure, depending on sun intensity (latitude, time of year) and skin pigmentation (people with darker skin may need 5-10 times longer sun exposure to generate the same vitamin D).[1,13] One expert recommends "sensible sun exposure" as an important adjuvant to vitamin D supplementation; such exposure, from either sunlight or ultraviolet radiation (tanning beds), would involve 5-30 minutes to arms and legs twice weekly between the hours of 10 am and 3 pm while wearing sunscreen on the face.[1] A recent attempt to quantify the vitamin D production from sun exposure at different times of the day, at different latitudes, and in people with different amounts of skin pigmentation, found too much variation in vitamin D produced to accurately predict whether an individual would meet official recommendations of daily vitamin D needs, leading the authors to favor vitamin D supplementation.[14] It is, of course, important to avoid excessive sun exposure, especially that which would lead to a sunburn, due to the well-known concerns about skin cancer. Of note, most experts recommend against direct sun exposure for children under the age of 6 months; for this demographic, vitamin D supplementation by itself is the best option.

Adverse Effects

Gastrointestinal effects and renal calculi continue to be mentioned as statistically more likely in vitamin D treatment groups than placebo groups.[10] The statistically significant increase in renal calculi from hypercalcemia appears to be more of a concern in groups treated with alfacalcidol and 1,25-dihydroxyvitamin D.[9,10] The ceiling above which dosing becomes unsafe is still being debated in the medical literature. Some researchers argue that the much-mentioned safety level of 2,000 IU daily does not apply to vitamin D2, due to its decreased potency.[3] Hypercalcemia and hyperphosphatemia have been demonstrated in people taking 50,000 IU daily, though 10,000 IU D3 daily (for 5 months) in adults appears to be safe.[1]

Annual bolus dosing may not be safe in some populations. One study in 2,258 women older than age 70 randomized to a single oral dose of 500,000 IU D3 annually in autumn or winter vs. placebo found that the treatment group had an increased risk of both falls and fractures.[15]

Summary

A few summary points can be culled from this overview of vitamin D dosing:

- Current DRIs are too low for general vitamin D maintenance dosing; 800-1,000 IU D3 is better for avoiding vitamin D deficiency and maintaining adequate levels.
- Some bolus dosing regimens may provide a more cost-effective, convenient approach to vitamin D repletion and maintenance, though single annual treatments may not be safe for all populations.
- For supplementation, vitamin D2 and D3 are more desirable in their efficacy and lack of side effects as compared to 1-alpha-hydroxy- and 1,25-dihydroxyvitamin D.
- A few trials, requiring further substantiation, seem to indicate that:
  - Oral and intramuscular dosing are probably similar in their ability to raise serum 25(OH)D.
  - Vitamin D3 is more potent than vitamin D2 in its ability to raise serum 25(OH)D.
- Including calcium with vitamin D regimens is necessary for the prevention of fractures.

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Vitamin D and Pain: Making Sense of It All

By Nancy J. Selfridge, MD

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An association between bone disease due to vitamin D deficiency (i.e., osteomalacia and pain) has long been established. However, despite epidemiologic studies associating painful conditions with season and latitude, research on vitamin D and pain is confusing.

Clinical Studies

In 1991, Gloth et al reported hyperesthesia in five patients with pain aggravated by light touch and minimal movement. These symptoms resolved in all patients after vitamin D therapy was instituted but returned when therapy was discontinued, prompting the authors to question whether vitamin D deficiency is associated with a pain syndrome.[1] Supporting this view is a study conducted at an inner city clinic in Minnesota by Plotnikoff et al, which showed the presence of hypovitaminosis D in 93% of the adults and children presenting with chronic pain.[2] This report sparked a passionate editorial debate about vitamin D deficiency and pain, unfolding over the following year in the *Mayo Clinic Proceedings*.

A 2009 review identified 22 studies that reported mean 25-OH vitamin D levels and/or investigated the results of vitamin D treatment in patients with chronic pain. These included five randomized double-blind trials of vitamin D treatment, two randomized but not double-blind studies, and several observational studies and case series reports with and without evaluation of vitamin D treatment. The authors concluded from their analyses of these studies that there is no convincing evidence of a link between chronic pain and vitamin D.[3] The same authors published in January 2010 a Cochrane review of vitamin D for the treatment of chronic painful conditions and once again concluded that the evidence base for the use of vitamin D for chronic pain in adults is poor.[4]

Discussion

There are several problems with the existing research on vitamin D and pain. It is admittedly seductive to think about a link between the two because of the attractiveness of having a simple, inexpensive, low-risk, and natural treatment for a condition that is so costly and creates so much human suffering. However, chronic pain is complex and vitamin D is not well understood as a drug, nor is it actually a vitamin per se. For example, we talk about "vitamin D deficiency," but rarely (if ever) "drug deficiency," and there are no natural food sources that are high in vitamin D. Furthermore, when attempting to draw conclusions from these studies, a number of questions need to be addressed, e.g., the form of vitamin D administered, whether appropriate dissolution studies were conducted with the product to determine oral bioavailability, whether patients were grouped into those with peripheral pain, visceral pain, and neuropathic pain, and whether any patients in the study were using drugs that reduce the absorption of fat-soluble vitamins.

Cholecalciferol, which is made in human skin by the sun or can be taken as an oral supplement, is the precursor for calcidiol (25-OH vitamin D). 25-OH vitamin D is the human substrate for calcitriol (1,25-OH2 vitamin D), a potent pleiotropic secosteroid hormone with multiple autocrine functions working primarily through effects on gene transcription in human tissues and organs. We know now that vitamin D insufficiency, defined by serum 25-OH vitamin D levels ≤ 30 ng/mL, is present in 90% of the dark skinned population and nearly 75% of the white population in the United States.[5] Identifying a control group for studies evaluating pain as a possible symptom of vitamin D insufficiency might prove complicated. Using vitamin D as a therapeutic agent is also fraught with challenges. Oral cholecalciferol (D3), in the doses defined by our current RDAs (200-400 IU), is simply not enough

to significantly alter serum levels in adults. Heaney et al have estimated that doses sufficient to provide enough substrate to fulfill all of the known human autocrine functions of vitamin D and to maintain D levels > 30 ng/mL in adults range from 3,000 to 5,000 IU daily.[6] Patients who are large, obese, elderly, or dark skinned may require even more daily vitamin D to maintain blood levels > 30 ng/mL. However, the U.S. Institute of Medicine maintains an Upper Limit (UL) recommendation of 2,000 IU of D3 daily and states persistent concerns about vitamin D toxicity. It is likely that this UL continues to influence researchers in choosing doses of vitamin D for clinical trials. Thus, studies aimed at giving vitamin D for pain that ignore blood levels to check for repletion of D status simply do not consider what we now know about vitamin D physiology and pharmacokinetics.

Another problem may exist when vitamin D treatment is done using ergocalciferol (D2), which is a synthetic prescription product. Though this product does raise 25-OH vitamin D2 levels, this is not precisely the same vitamin D substrate that is made in human skin. While there is no evidence that D2 and D3 are not biologically equivalent, there is no evidence that they are biologically equivalent either. The two do appear to differ in their pharmacokinetics and potency.[7] As yet, the mechanisms that underlie any association between low vitamin D status and pain remain unidentified. Nor do we know what blood level of 25-OH vitamin D would be necessary for a reduction in pain in most people if the two were convincingly linked. At least some of the biologic effects of vitamin D appear to have thresholds for optimum dose-response. For example, levels needed to prevent rickets (10 ng/mL) are lower than levels needed to significantly suppress parathyroid hormone (20 ng/mL) or to maximize intestinal calcium absorption (34 ng/mL).[8] Thus, simply raising 25-OH vitamin D above deficiency levels of 10-20 ng/mL may not be enough to assess for a pain-alleviating effect.

Conclusion

For the time being, in clinical practice it may be helpful to look at pain as a possible harbinger of low vitamin D status, just as fatigue can be a harbinger of hypothyroidism. Most people with fatigue will not have hypothyroidism. However, this fact does not dissuade us from screening for hypothyroidism and correcting it if need be. Similarly, if low vitamin D status is found in patients with pain, correcting the D status may result in less pain, or for some, complete improvement. But correcting D status, or "repleting" vitamin D, is the prime directive, and research suggests that the benefits beyond possible pain relief may be substantial, including a reduction in risk of mortality.[9] Until we have better guidelines to inform our standard of care, clinicians will have to monitor 25-OH vitamin D blood levels to ensure that patients achieve sufficiency (> 30 ng/mL, according to most vitamin D experts) and then maintain repletion throughout the year.

There thus remains a dire need for studies to convincingly link vitamin D levels to the different types of pain, and to discern a mechanism or mechanisms for vitamin D in chronic pain pathophysiology, as each type is associated with different neural pathways and mechanisms at the receptor level. ■

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Requiring Attention: Pesticides and ADHD

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Source: Bouchard MF, et al. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. *Pediatrics* 2010;125:e1270-1277.

Synopsis: *Using NHANES data from 2000 to 2004, researchers collected and analyzed information on urinary organophosphate pesticide metabolite levels and children with a diagnosis of ADHD, as well as ADHD subtypes. They found that children with higher levels of*

pesticide residue in their urine were more likely to have a diagnosis of ADHD. One of the distinctive aspects of this study is that it focused not on high-risk populations, but on the U.S. population in general and, thus, common degrees of pesticide exposure, most probably through food. The results, however compelling, do not in and of themselves indicate causality.

The investigators' purpose was to examine the relationship between urinary concentrations of dialkyl phosphate (DAP) metabolites of organophosphate pesticides and attention deficit/hyperactivity disorder (ADHD) in children 8-15 years of age. Cross-sectional data from the 2000-2004 National Health and Nutrition Examination Survey (NHANES) were available for 1,139 children (during this specific NHANES time frame, ADHD was assessed in children aged 8-15). Participating children were assumed to be representative of the general U.S. population because NHANES is a population-based health survey of non-institutionalized U.S. residents. Participants completed household surveys, and blood and spot urine samples were collected during physical examinations at mobile centers. Urinary DAP metabolite levels were measured for a random sub-sample. A structured diagnostic interview (DISC-IV, which helps identify subtypes of ADHD) with a parent or caretaker by phone was used 2-3 weeks following the physical examination to ascertain ADHD diagnostic status on the basis of modified DSM-IV criteria. The investigators also conducted analyses in which a diagnosis of ADHD was defined as either meeting DISC-IV diagnostic criteria for ADHD or a child having regularly taken medications for ADHD during the previous year. Urine samples were frozen, stored, and sent to the Centers for Disease Control and Prevention's (CDC's) National Center for Environmental Health where testing for 6 urinary DAP metabolites, resulting from the degradation of a variety of organophosphates, was performed (3 dimethyl alkylphosphate molecules [DMAP, such as malathion] and 3 diethyl alkylphosphate [DEAP, such as chlorpyrifos] molecules were measured). Individual urinary DAP metabolite levels were below the analytical limits of detection for many of the subjects, so additional analyses on the metabolite with the highest detection frequency (dimethyl triphosphate) were performed. Analyses accounted for the impact of potentially confounding variables such as gender, race/ethnicity, self-reported family income, blood lead concentrations, and maternal age at birth.

A total of 119 children met diagnostic criteria for ADHD, this corresponding to a population prevalence of 12.1% (the inclusion of children taking ADHD medications raised the total number of ADHD cases to 148). Subtype prevalence estimates were 7.6% for inattentive subtype, 1.5% for hyperactive/impulsive subtype, and 3.0% for combined ADHD subtype.

Almost all children (93.8%) had ≥ 1 detectable DAP metabolite. The odds of meeting DISC-IV criteria for ADHD increased with increasing urinary concentrations of total DAP metabolites. For the most commonly detected DMAP metabolite, dimethyl thiophosphate, which was identified in 64.3% of children, those with levels higher than the median detectable concentrations had twice the odds of ADHD (adjusted odds ratio [AOR], 1.93; 95% confidence interval [CI], 1.23-3.02) compared with children with undetectable levels. Adjustment for covariates attenuated the estimates but they remained statistically significant. When children taking ADHD medications were included, higher effect estimates were obtained for DMAPs (AOR, 1.72; 95% CI, 1.31-2.28). Associations between DMAP levels and ADHD were similar for girls and boys.

The researchers closed by summarizing their findings: Children with higher urinary levels of organophosphate metabolites, reflecting levels of exposure common among U.S. children, are more likely to meet the diagnostic criteria for ADHD. They called for prospective studies to determine whether the association between organophosphate exposure, especially from but not limited to specific food consumption, and ADHD might be causal.

■ COMMENTARY

A growing number of studies have raised the specter of environmental toxin exposure playing a significant role in the development of specific diseases, including cancer and Parkinson's disease. With regard to behavioral issues in children and specific exposure to organophosphate pesticides, prior investigations have focused mainly on populations known to have exposure levels higher than the general population. Results of such studies largely showed that childhood exposure to organophosphates was associated with negative impacts on neurobehavioral development, including poor cognition. The current paper is perhaps the first to consider the risk of "average" organophosphate exposure.

Children seem to be at high risk from organophosphate toxicity because the developing brain is more susceptible to neurotoxicants, the dose of pesticides per body weight is likely to be larger, and children have reduced expression of detoxifying enzymes.

The study can be dinged for using but a single spot urine test to determine level of organophosphate exposure, but the authors point out that since organophosphates are cleared from the body within 6 days, the relatively consistent presence of metabolites in the subjects' urine implies continued exposure, suggesting that exposure is likely coming from the diet so long as that diet has been consistent. The EPA considers food, drinking water, and residential pesticide use significant potential sources of expo-

sure. Residential pesticide use is common, but the major source of exposure to pesticides for infants and children is through the diet, according to the National Academy of Sciences. For example, the 2008 U.S. Pesticide Residue Program Report indicates that malathion was detectable in 28% of frozen blueberry samples, 25% of strawberry samples, and 19% of celery samples. The study authors quote data suggesting that disruptions in cholinergic signaling may occur with ADHD (organophosphates inhibit acetylcholinesterase). Organophosphates are among the most commonly used pesticides.

Considering that the President's Cancer Panel recently released information tying various environmental chemicals to an increased risk of cancer, and that articles on toxic hazards have been appearing in lay publications like *Time* magazine and *The New Yorker*, practitioners can expect questions about environmental health hazards from their patients to increase and concern a widening array of topics. In particular, the topic of pervasive developmental disorders in children is an understandably emotional one, perhaps made even more so by the results of studies like the one addressed here that suggests pesticide exposure may contribute to developmental disorders.

Practitioners are often left in the unenviable position of explaining that "We don't know why ADHD occurs" — now made all the more so because if these data pan out we may indeed understand a potential contributing factor to the development of ADHD but have little in our arsenal to recommend either for prevention or treatment. Recommend strictly organic foods? That knocks out most of the population due to issues of either access or expense. Perhaps what data like these provide practitioners is added motivation to act as a cohesive unit concerned with public health and demand greater regulation of the food industry. Until such time we may all be at risk. ■

The Effect of St. John's Wort on Hot Flashes in Women

ABSTRACT & COMMENTARY

By Judith L. Balk, MD, MPH, FACOG

Dr. Balk is Associate Professor, Magee-Women's Hospital, University of Pittsburgh; she reports no financial relationship to this field of study.

Synopsis: *One hundred women with hot flashes, aged 45-55, were randomized to receive St. John's wort (SJW) or placebo for 8 weeks. At 4 weeks, the frequency and severity of the hot flashes were better in the treatment group than in the placebo group, whereas the duration of hot flashes was the same in both groups. At 8 weeks, severity, frequency, and duration were better in the treatment group than in the placebo group. However, both groups improved over time, relative to baseline.*

Source: Abdali K, et al. Effect of St John's wort on severity, frequency, and duration of hot flashes in premenopausal, perimenopausal and postmenopausal women. *Menopause* 2010;17:326-331.

Estrogen levels decline in premenopausal, perimenopausal, and postmenopausal women, causing vasomotor symptoms. The objective of this study was to assess the effects of SJW on hot flashes. One hundred women from an academic health center in Iran were recruited to participate in this study. Subjects were randomized to receive either SJW or placebo for 8 weeks. The trial interventions were drops containing either placebo or SJW extract (Hypiran, Poursina Pharmaceutical Mfg Co., Tehran, Iran). The SJW drops contained hypericin 0.2 mg/mL, and placebo was distilled water; the drops were identical in smell, color, and taste. Subjects were advised to take 20 drops of the medicine, three times per day, for 2 months. Blatt-Kupperman Index, a validated scoring of menopausal symptoms, was the primary outcome variable. Average age of the subjects was 50.4 years. Both groups improved over time, and the difference from baseline for each group was statistically significant. The difference between the groups in the duration of hot flashes was not different at 4 weeks, but it was improved at 8 weeks in the treatment group compared to the placebo group. Both severity and frequency of hot flashes were improved at both 4 and 8 weeks in the treatment group compared to the placebo group.

■ COMMENTARY

The design and methodology of this study are excellent; it is randomized, double-blind, and placebo-controlled. Intention-to-treat was used as the primary analysis. Loss to follow-up was minimal, and a power analysis was presented. The method of randomization is described; a random table was used, but allocation concealment was not described.

Within this excellent design, however, some limitations are noted. The study enrolls premenopausal, perimenopausal, and postmenopausal women with hot flashes; definitions are given for each group, and the age range of the subjects was 45-55 years. This age range is appropriate, but one may question if they were able to differentiate between premenopausal and perimenopausal women based on their definitions. Interestingly, the conclusion given by the authors is that SJW can be used as an effective treat-

ment for the vasomotor symptoms of perimenopausal or postmenopausal women. No mention of premenopausal women is noted in the conclusion, but the text does not describe differences in effectiveness between the menopause categories.

Another limitation is that the eligibility criteria are confusing. For instance, women were included if they were having untreated complaints for at least 2 months, but excluded if they had had any treatment to alleviate climacteric symptoms in the last 12 weeks before study entry. Two different eligibility criteria describe the frequency of hot flashes: One criterion is that they must be experiencing moderate-to-severe hot flashes at least once per day, and a different eligibility criterion is that they must be having three or more hot flashes per day. One would assume that the population must be having three or more hot flashes per day, with at least one of these being severe.

Compared with other hot flash studies, the frequency and severity of the hot flashes are rather small, and one might question whether the ceiling effect may play a role. If the subject is only having three hot flashes per day, with two of those being mild, how much better can she get? Justification for these eligibility criteria is not stated.

Lastly, smoking, drinking alcohol, and drinking caffeine excluded participation in this study; generalizability may come into question based on these exclusion criteria. Overall, the study population, design, methods, and analysis are appropriate.

The treatment intervention is appropriate, but likely not for the reasons that the authors state. The authors repeatedly note that SJW is a phytoestrogen, and that the phytoestrogenic activity may be the mechanism of improving menopausal symptoms caused by "a decline in estradiol levels." The references in the paper that indicate that St. John's wort is a phytoestrogen are both textbook references, not original research. It is unlikely that original research demonstrating that the mechanism of action of St. John's wort is phytoestrogenic activity would be presented first in a textbook. The Natural Medicines Comprehensive Database does not list phytoestrogenic or sex hormone effects as a mechanism of action for St. John's wort.[1]

St. John's wort is best known for its effects on mild-to-moderate depression,[2] and it likely has serotonergic effects, inhibiting uptake of serotonin, dopamine, and norepinephrine.[1] It would make sense that a botanical that has similar pharmacologic effects to a serotonin and norepinephrine reuptake inhibitor like venlafaxine might be beneficial for vasomotor symptoms, since venlafaxine is effective for hot flashes.[3] Thus, SJW might be effective both for vasomotor symptoms such as hot flashes, and for mild-to-moderate depression occurring in menopause, but the mechanism of action is not likely via sex hormone pathways.

While the purported mechanism of action may not be highly relevant in the face of positive outcomes, one statement that the authors make in the background section is concerning. The authors note that St. John's wort "contains compounds called phytoestrogens, which can be used as an alternative to estrogen in women having a contraindication to use of female sex hormones." This statement is referenced with a chapter in a nursing textbook.[4] However, the safety of phytoestrogens, such as soy, in hormonally sensitive conditions such as breast cancer is unknown.[5-7] The authors also note that phytoestrogens "have molecular components that are identical in structure and function to human hormones." Thus, it would be unclear why phytoestrogens, if they are identical in structure and function to human hormones, would be able to be used if there is a contraindication to use of hormones. Because SJW is likely not a phytoestrogen, it could potentially be used in women with hormonally dependent conditions.

One must keep in mind that SJW is associated with important herb/drug interactions. It is a potent inducer of some cytochrome P450 enzymes, resulting in increased metabolism and reduced plasma concentrations of many drugs, including cyclosporine, indinavir, and amitritpyline.[1] Importantly, SJW also increases the metabolism of the estrogen and progestin in oral contraceptive pills.[1,8] St. John's wort is associated with breakthrough bleeding, follicle growth, and probable ovulation. Thus, women of childbearing age who are using oral contraceptives should be cautioned that St. John's wort might interfere with contraceptive effectiveness.[8]

In conclusion, SJW might be helpful for vasomotor symptoms in women age 45-55. Longer-term studies would be helpful to delineate the risks and benefits over the many months and years that menopausal symptoms can occur. ■

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Mood Munchies: Chocolate and Depression

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *Increased intake of chocolate was associated with higher rates of depression on a mood screening instrument in this cross-sectional study. Whether cause and effect or self-treatment, the generally accepted idea that chocolate is comfort food appears in doubt.*

Source: Rose N, et al. Mood food: Chocolate and depressive symptoms in a cross-sectional analysis. *Arch Intern Med* 2010;170:699-703.

The authors of this cross-sectional study gleaned data from an independent investigation of the noncardiac effects of lowering cholesterol levels to explore the relationship between chocolate consumption and depressed mood in adults. Initially, 1,018 people in San Diego aged 20-85 years (694 men; mean age, 58 years; mean BMI, 27.8 kg/m^2; > 50% college graduates) were screened for participation in the trial, of which 1,009 completed a study-specific "Statin Study Questionnaire" chocolate consumption (SSQ-C) question: "How many times a week do you consume chocolate?" A small number (n = 78; 35 men) were taking antidepressant medication and were subsequently removed from consideration, such that the primary analysis focused on data from 931 participants.

Subjects completed the Center for Epidemiological Studies-Depression Scale (CES-D), a validated screening instrument related to mood. A score ≥ 16 was considered positive and used as a cutoff; a second cutoff of 22 was used to signify the possible presence of major depression.

A Food Frequency Questionnaire specific to chocolate intake (FFQ-C) was used; a medium serving was considered 1 ounce (28 g) of chocolate candy. Proportionately, a small serving was deemed equal to one-half a medium serving, and a large serving equal to 1.5 medium servings. Responses were converted to per-month consumption to provide a unified metric. Frequency (times/month) and rate of chocolate consumption (servings/month) were captured using the FFQ-C, while frequency (times/week) was determined with the SSQ-C. A number of other foods and specific nutrients were analyzed to assess for specificity of findings associated with chocolate intake.

Participants' mean CES-D score was 7.7 (range, 0-45). Mean chocolate consumption values were 6.0 medium servings/month and 6.0 times/month per responses to the FFQ-C, and 2.0 servings/week according to SSQ-C results. Those subjects with a CES-D score ≥ 16 reported significantly higher chocolate intake than those with lower CES-D scores (findings significant for FFQ-C times/month, FFQ-C servings/month, and SSQ-C times/week). Significance of the findings was evident with a cutoff point of 16, as well as with a cutoff of 22, and the findings were independently significant for men and women. The findings were not influenced by differential intake of high-antioxidant or other types of foods or caffeine ingestion, and BMI did not vary by CES-D score. The authors concluded that people with higher depression rating scores consume greater amounts of chocolate.

■ COMMENTARY

People commonly joke about turning to chocolate as "comfort food," a perspective that seems well-ingrained in society but one lacking significant supportive data.[1] On the flip side, a few studies have found high rates of chocolate consumption to be associated with worsened mood, and one study looking at groups of people reported an increased suicide rate.

It's important to remember that the investigation was designed with a completely different purpose in mind, and that it is cross-sectional in nature, so causality cannot be assumed. The authors were forthright in pointing out these limitations, as well as the fact that a positive score on the CES-D is not strictly equivalent to a clinical diagnosis of depression, and that different chocolate products contain myriad constituents. Still, the strengths of the study findings are formidable, with consistent findings for both men and women, and analyses suggesting specificity of the chocolate-related results.

The authors posit that a depressed emotional state could trigger chocolate cravings as self-treatment; that, like alcohol, chocolate could offer initial benefits but long-term challenges to mood; and the possibility that specific physiologic changes could drive both chocolate cravings and depression. Regardless, it is intriguing (if not dispiriting…) to consider that frequent chocolate ingestion may not be a reasonable treatment for the blues, and might even contribute to them. Such sobering news needs to be appropriately confirmed, of course, but com-

pels me to reach for a small piece of dark chocolate. Perhaps I should hold off, but I'm going to rationalize that it's good for my heart. ■

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Religious Involvement and Infectious Disease

ABSTRACT & COMMENTARY

By Howell Sasser, PhD

Dr. Sasser is Associate Professor of Epidemiology, New York Medical College, Valhalla, NY; he reports no financial relationship to this field of study.

Synopsis: *Gillum and Holt assessed the prevalence of six infections by frequency of attendance at religious services. Although results varied by race/ethnicity and factors related to sexual and drug-use practices, there appeared to be lower prevalence among those attending more often. Although these results are weakened by certain methodological issues, they provide evidence that religious practice plays a role in limiting risky behavior.*

Source: Gillum RF, Holt CL. Religious involvement and seroprevalence of six infectious diseases in US adults. *South Med J* 2010;103:403-408.

A KEY OBJECTIVE OF CONTINUING INTEREST IN THE STUDY OF religion and health is the teasing out of the constituent parts of the construct "religiousness." The observation that those who are more religiously active are also healthier in some respects than those who are not begs the question: What aspect of religion is the "active ingredient?"[1] A prime candidate in the context of some disease processes is the inhibitory effect of religion on risky behaviors. This appears particularly relevant where infectious, especially sexually transmitted, diseases are at issue.

Gillum and Holt used a large cross-sectional database to assess the co-prevalence of religious involvement and several infectious agents. They drew their population from the Third National Health and Nutrition Examination Survey (NHANES III), an ongoing health surveillance project of the U.S. Department of Health and Human Services. NHANES III collected data between 1988 and 1994, and used both questionnaires and collection of biological samples to assess the health states of respondents.

Religious activity was measured with a single question about frequency of attendance at religious services (categorized for analysis as Never, Less than weekly, Weekly, and More than weekly). Serologic data were available for hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), herpes simplex virus type 2 (HSV-2), *Toxoplasma gondii*, and *Helicobacter pylori* (for the period 1988-1991 only). Selected potentially confounding factors, including level of education, geographic region, marital status, drug use, number of sexual partners, and overall health, were also used in the analysis.

Of 33,994 NHANES III participants with baseline data, 11,507 met age and data completeness criteria and were included in Gillum and Holt's analysis. In the total population, seroprevalence of HSV-2 and HCV was statistically significantly higher in those who never attended religious services as compared with those who attended with any frequency. Seroprevalence of HBV was higher in never-attenders in the White, Black, and Mexican-American

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

25. Vitamin D deficiency is strongly linked to generalized physical pain, based on the available research evidence.
a. True
b. False

26. SJW may interact with which of the following medications?
a. Cyclosporine
b. Indinavir
c. Amitritpyline
d. All of the above

27. Religious practice influences the prevalence of some infections by which of the following mechanisms?
a. Augmentation of immune function through stress reduction
b. Inhibition of risky behavior
c. Emphasis on negative coping strategies
d. Provision of non-traditional medical services

Answers: 25. b, 26. d, 27. b.

subpopulations. After adjustment for drug use and sexual behavior, the association of religious activity with HSV-2 and HBV became non-significant among the White and Black respondents, though not among the Mexican-Americans. The association with HCV was more robust even after adjustment. No significant association of religious activity with the enteric pathogens was observed.

■ COMMENTARY

Gillum and Holt offer a partial answer to the question of how religious activity influences a group of health conditions. There appears to be evidence that some element of religious behavior, most likely inhibition of risky behavior, results in lower prevalence of some infectious agents among religiously active people. This inference is strengthened by the apparent attenuation of the effect of attendance at religious services after controlling for factors associated with sexual and substance abuse-related risk. However, variations in the degree of protectiveness by race/ethnicity make clear that the effect is not monolithic, and that other cultural factors, such as strength of family structures and gender role norms, may represent unmeasured confounders. A number of other issues are worth noting.

The cross-sectional design of the study leaves doubt as to the sequence in time of events. The desired inference is that religious involvement preceded exposure (or the potential for exposure). However, it is also plausible that exposure came first, and perhaps even that it influenced subsequent religious behavior. It is also not possible to locate in time the other factors that were shown in this study to be associated with religious involvement, seropositivity, or both. This limits the strength of the study's findings to suggestion of a relationship that requires further study.

The use of frequency of attendance as the measure of religiousness was dictated by what was originally collected by NHANES, but is not reflective of current practice in this area of research. A number of more complex instruments measuring beliefs and individual spiritual practices, as well as participation in organized religious services, has been proposed.[2-4] These measures avoid the potential bias created by a "healthy worshiper effect" — the difficulty in sorting out whether those engaged in public activities are healthier as a result, or if those not so engaged are prevented from doing so by poor health.

A positive aspect of this study was the inclusion of both infections generally regarded as venereal (HSV-2, HBV) and others not usually so characterized (HAV, *H. pylori*, *T. gondii*). (HCV has, as it were, a foot in both camps.) The finding that the results were mixed for the venereal agents, but uniformly negative for the enteric agents, suggests that inhibition of certain high-risk behaviors may be a key component of the observed effect of religion on health. The timing of data collection for this study (1988-1992) may explain the otherwise odd absence of HIV, which at the time (pre-HAART) was treated as an acute, or at least rapidly progressing, infection. However, the stigma attached to HIV infection, and the frequency of HIV co-infection with other viral and bacterial pathogens, leaves the reader of the present study uneasy as to the possible unmeasured effect of HIV on its findings.

The study's focus on viral agents is understandable. They are generally persistent and allow for stable measurement of population prevalence. Because they are less easily cleared from the system than are bacterial pathogens, they also are more urgent targets for effective prevention strategies. Presumably, the inhibiting effect of religious belief on behavior means that exposure to all agents is reduced equally, but this cannot be inferred from the present study. ■

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The essential monthly primary care update

By Louis Kuritzky, MD

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Coronary Calcium Scores enhance risk prediction

Source: Polonsky TS, et al. *JAMA* 2010; 303:1610-1616.

PROBABLY THE MOST WIDELY RECOGNIZED scoring system for predicting CV risk is the Framingham Risk Score (FRS). The United States Preventive Services Task Force (USPSTF) has recently published the opinion that novel risk markers such as C-reactive protein do not sufficiently enhance risk prediction enough to justify their routine utilization in addition to traditional scoring systems like FRS Coronary Calcium Score (CCS) has a number of appealing attributes that suggest consideration as a powerful prediction tool.

In the Multi-Ethnic Study of Atherosclerosis (MESA) trial of persons without known CHD at baseline, a CCS > 300 was associated with a 10-fold increased risk for CHD events. A critical issue, however, is whether new or additional prediction score tools add meaningfully to existing methods. A metric known as Net Reclassification Improvement (NRI) has been recently proposed to distinguish whether the incremental impact of a scoring system or risk factor upon already existing methods is meaningful.

Using the cohort of MESA (n = 6814 adults; age > 45), Polonsky et al compared risk prediction as derived from FRS vs FRS + CCS. The addition of CCS to FRS resulted in a statistically significant NRI. An additional 23% of persons who experienced CHD events but had not been identified by FRS as high risk were correctly reclassified by the addition of CCS. Similarly, an additional 13% of subjects not classified by FRS as low risk (and who did not suffer events), were reclassified as low risk by the addition of CCS. Whether the preferential (or additional) use of CCS for risk prediction can improve outcomes over traditional risk scores alone will require further definition, although many are already sufficiently encouraged by the predictive power of CCS to currently employ it. ■

Exacerbations of COPD: Not so innocent

Source: Donaldson GC, et al. *Chest* 2010;137:1091-1097.

ACUTE EXACERBATIONS OF COPD (AE-COPD) are sometimes misconstrued as minimally consequential "bumps in the road" along the journey of progressive COPD. Unfortunately, the toxicity of ae-COPD has been underappreciated; ae-COPD are associated with hospitalizations, loss of lung function that is typically not regained, and mortality. Donaldson et al direct our attention to a newly recognized additional burden of morbidity associated with ae-COPD: MI and stroke.

The Health Improvement Network (THIN) database contains anonymized medical records of patients seen by GPs in England and Wales. Over a 2-year period, 25,857 COPD patients provided a dataset with which to compare the incidence of MI and stroke during "stable" periods of COPD with the immediate post-ae-COPD period.

The incidence of acute MI was increased more than 2-fold in the 5-day period immediately following an ae-COPD; similarly, stroke incidence was increased more than 2-fold in the 49-day period immediately post-ae-COPD. Both findings were statistically significant.

No pharmacologic treatment of COPD has been proven to be disease-modifying. Yet, since various pharmacotherapies have been shown to reduce ae-COPD, perhaps such treatments will ultimately be shown to impact disease outcome by affecting the above-mentioned consequences of ae-COPD: increased stroke and MI. ■

Vitamin E, but not pioglitazone, improves NASH

Source: Sanyal AJ, et al. *N Engl J Med* 2010;352:1675-1685.

STEATOSIS IS THE ACCUMULATION OF FAT, derived primarily from triglycerides in hepatic cells. Progressive steatosis can lead to hepatic inflammation, which, when not associated with alcohol, is known as non-alcoholic steatohepatitis (NASH). Obesity and diabetes are the two conditions most commonly associated with NASH. Because as many as 15% of NASH cases may ultimately progress to cirrhosis, effective treatments are eagerly sought.

Since the pathologic underpinnings of NASH often include insulin resistance, hypetriglyceridemia, and type 2 diabetes, pharmacology with thiazolidinediones (TZD) appears logical. Unfortunately, results from pilot trials of TZDs have been conflicting.

The NASH Clinical Research Network, established by the NIDDK, conducted a

placebo-controlled trial of pioglitazone or vitamin E in non-diabetic NASH patients (n = 247). Subjects received 800 IU/d vitamin E, 30 mg/d pioglitazone, or placebo for approximately 2 years. The primary outcome was histologic status of NASH.

At 96 weeks, vitamin E did demonstrate a statistically significant rate of NASH histologic improvement, but pioglitazone did not. Even though there were some favorable histologic effects, neither intervention showed a reduction in hepatic fibrosis, so we remain uncertain about whether vitamin E can impact the development of serious long-term liver disease. Pioglitazone did not achieve an effect on the primary outcome, but explanations for why TZDs may still be considered for NASH therapy are presented by the authors. ■

Best use of home BP monitoring

Source: Pickering TG, et al. *J Am Soc HTN* 2010;4:56-61.

The largest body of information guiding treatment of hypertension (HTN) is based upon office BP management. Nonetheless, home BP monitoring (HBPM) is documented to be a better predictor of CV risk than office BP. For instance, patients with high office BP but low HBPM are recognized to be at substantially lower risk than office BP predicts; similarly, high HBPM pressures compared to office BP portends greater risk than indicated by office BP alone. Simply the fact that HBPM offers the opportunity for many more BP readings than is readily accessible in clinical care provides both a more comprehensive and consistent BP profile.

Recording HBPM twice daily (morning and evening), when averaged over 1 week, provides a sufficient BP profile to help guide management. By HBPM, HTN is > 135/85 mmHg and normotension is < 125/75 mmHg. Borderline HBPM (125-135/75-85 mmHg) merits consideration of 24-hour ambulatory BP monitoring for further clarification. The authors, writing on behalf of the American Society of Hypertension, provide a list of validated home BP monitoring devices at: www.dableeducational.org/. ■

Suicide risk with anticonvulsants

Source: Patorno E, et al. *JAMA* 2010;303:1401-1409.

Although the term "anticonvulsant" is indicative of a therapeutic class, pharmacologically the class is diverse. Despite dissimilarities, an analysis by the FDA (2008) discerned a relative doubling of suicide behavior/ideation in anticonvulsant recipients compared to placebo, resulting in a change in labeling.

The HealthCore Integrated Research Database provides data with which to assess the relative risk for suicidal acts in persons receiving a variety of anticonvulsant agents. During a 5-year interval (2001-2006), almost 300,000 new prescriptions for various anticonvulsants were documented in this population. When compared to treatment with either topiramate or carbamazepine (reference drugs), important distinctions emerged in reference to suicidal acts and violence. For instance, the hazard ratio for suicidal acts was 1.42 for gabapentin, 1.84 for lamotrigine, and 1.65 for valproate, compared to topiramate.

The mechanism by which some anticonvulsants incur an increased suicide risk is not known, despite the recognition that anticonvulsants can have impact upon mood. The first 2 weeks after initiation is recognized to be a higher risk period. Clinicians should be vigilant for behavior or mood changes in patients treated with anticonvulsants, noting lesser apparent risk for topiramate or carbamazepine. ■

For type 2 diabetes, after metformin, what next?

Source: Phung OJ, et al. *JAMA* 2010;303:1410-1418.

In the absence of contraindications, metformin is the preferred initial treatment for most patients with type 2 diabetes (DM2). Unfortunately, monotherapy is unlikely to maintain adequate glycemic control, requiring additional treatment. Although the addition of insulin to metformin is an appropriate next step, and has been labeled Tier 1 in the most recent guidelines published by the American Diabetes Association, some patients are reluctant to use insulin, and the considerable weight gain experienced by some insulin users, as well as risk of hypoglycemia, is problematic.

Among the non-insulin therapeutic choices, there is a great degree of variation in tolerability issues, such as amount of weight gain and frequency/severity of hypoglycemia that may help guide treatment decisions. Phung et al analyzed data from 27 randomized controlled trials (n = 11,198), most of which were 6 months or less in duration, to compare weight changes and hypoglycemia when non-insulin agents were added to metformin.

As might be anticipated, when TZDs, sulfonylureas, and glinides were added to metformin there was a 1.8-2.1 kg weight gain. GLP-1 mimetics, alpha-glucosidase inhibitors, and DPP-4 inhibitors were either weight neutral or associated with minimal weight loss. Sulfonylureas were associated with higher rates of hypoglycemia.

Of course, progressive treatment of DM2 must be individualized, and should include consideration of characteristic tolerability issues such as weight gain and hypoglycemia. ■

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PPIs, *Clostridium difficile*, and Bone Fractures

In this issue: *New reports about proton pump inhibitors and the effects of gastric suppression, pioglitazone vs vitamin E for non-alcoholic steatohepatitis, metformin and vitamin B12 deficiency, and FDA Actions.*

PPIs, C. difficile, and bone fractures

Since H2 antagonists were introduced 30 years ago followed by proton pump inhibitors (PPIs) 20 years ago, there has been speculation whether long-term gastric acid suppression might have adverse effects. Billions of doses later, there is new evidence that chronic PPI use may lead to infections, especially *Clostridium difficile* infection (CDI), and may also contribute to bone fractures.

In the first of several studies published in the May 10 issue of *Archives of Internal Medicine*, researchers looked at more than 101,796 discharges from a tertiary care medical center during a five-year period, reviewing the level of acid suppression therapy and its relationship to CDI. As the level of acid suppression increased, the risk of CDI increased from 0.3% in patients not receiving acid suppressive therapy to 0.6% in those receiving H2 antagonists to 0.9% in those receiving daily PPIs and finally 1.4% in those receiving high-dose PPI therapy. After adjustment for a number of factors including comorbid conditions, age, and antibiotic use, the odds ratio for CDI infections were: 1 with no acid suppressing treatment, 1.53 (95% confidence interval [CI], 1.12-2.10) with H2 antagonist, 1.74 (95% CI, 1.39-2.13) with PPIs, and 2.36 (95% CI, 1.12-2.10) with high-dose PPI therapy. The authors conclude that increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C. difficile* infections, and the risk increases with more aggressive acid suppression (*Arch Intern Med* 2010;170: 784-790).

In a second study from the same journal, researchers from the VA system in Massachusetts performed a retrospective, cohort study of 1166 inpatients and outpatients with CDI to determine if PPI use affected recurrence rates. During treatment for CDI, 45% of patients received a PPI while 55% did not. Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.2%). The hazard ratio for recurrent CDI in those exposed to PPIs was 1.42 (95% CI, 1.11-1.82). The risk was higher in patients older than 80 years and in patients exposed to antibiotics not targeted to CDI infections The authors conclude that PPI use during treatment for CDI was associated with a 42% increased risk of recurrence (*Arch Intern Med* 2010;170:772-778).

It has also been postulated that suppressing gastric acid may affect digestion and absorption of certain nutrients, specifically calcium. Although this has never been definitively proven, multiple studies have shown that chronic PPI use is associated with bone fractures. The most recent study, also published in the May 10 issue of *Archives of Internal Medicine*, was a prospective analysis of more than 160,000 women enrolled in the

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Women's Health Initiative study. In more than 1 million person-years of follow-up, there were 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and more than 21,000 total fractures. The multivariate-adjusted hazard ratios for current PPI use was 1 for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fractures, and 1.25 (95% CI, 1.15-1.36) for total fractures. Bone mineral density did not vary between PPI users and non-users. The authors conclude that use of PPIs in women was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures (*Arch Intern Med* 2010;170:765-771). This study confirms the findings of several large epidemiological studies that suggest that PPI use is associated with increased osteoporotic fracture risk. On May 25, the FDA issued a warning regarding the possible fracture risk associated with high-dose long-term use of PPIs. The Agency will require labeling changes to describe the possible risk.

As noted in these studies, PPI use is associated with risk of osteoporotic fractures and *Clostridium difficile* infections. Other studies have linked the PPIs to a higher risk of hospital- and community-acquired pneumonia, as well as enteric infection such as *Salmonella* and *Campylobacter* gastroenteritis. In an editorial in the May 10 issue of *Archives of Internal Medicine*, Mitchell Katz, MD, notes that of the more than 110 million prescriptions for proton pump inhibitors filled each year, many are for inappropriate indications, making PPIs one of the most overprescribed medication classes in the world. He suggests that "for most patients the adverse effects of PPIs outweigh the benefits" and urges physicians to offer other treatments for dyspepsia, prescribe shorter courses, and consider a trial of discontinuing PPIs in patients who are asymptomatic (*Arch Intern Med* 2010;170:747-748). ■

Pioglitazone vs vitamin E for NASH

Non-alcoholic steatohepatitis (NASH) is a common liver disease that is difficult to treat and often progresses to cirrhosis. A new study compares the thiazolidinedione pioglitazone (30 mg daily) to vitamin E (800 IU daily) in a placebo-controlled trial for 96 weeks in 247 nondiabetic NASH patients. The primary outcomes were standardized scores for steatosis, lobar inflammation, hepatocellular ballooning, and fibrosis as determined by liver biopsy. Vitamin E therapy was associated with a significant improvement in non-alcoholic steatohepatitis (43% vs 19%; $P = 0.001$), but pioglitazone did not show statistical improvement (34% vs 19%; $P = 0.04$). Serum transaminases improved with both treatments, and both reduced hepatic steatosis and lobular inflammation, but neither improved fibrosis. Pioglitazone caused significant weight gain compared to vitamin E or placebo. The authors conclude that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes (*N Engl J Med* 2010;362:1675-1685). ■

Metformin and vitamin B12 deficiency

Monitor your patients on metformin for vitamin B12 deficiency. This is the message of a recent study from the Netherlands. The study enrolled 390 patients with type 2 diabetes on insulin and initiated metformin 850 mg three times a day or placebo for an average of 4.3 years. Metformin treatment was associated with a mean decrease in vitamin B12 concentrations of 19% ($P < 0.001$) and an increase in homocysteine concentrations of 5% ($P = 0.091$). Longer-term treatment with metformin was associated with larger declines in vitamin B12 levels. The authors conclude that metformin likely causes malabsorption of vitamin B12 and recommends routine monitoring of vitamin B12 levels in patients who are treated with metformin (*BMJ* 2010;340:c2181). ■

FDA actions

The FDA has approved a new formulation of oxycodone (OxyContin®) that is designed to discourage chewing, crushing, or dissolving the drug. The FDA admits, however, that although the new formulation reduces the risk of snorting or injecting the drug, it can still be abused by simply ingesting larger doses than recommended. Vocal critics have called for oxycodone's withdrawal from the market due to an explosion in abuse of the drug nationwide and calls this new formulation "too little too late."

The FDA has recommended resuming use of Rotarix® rotavirus vaccine and to continue using RotaTeq® rotavirus vaccine. Rotarix was found to have elements of the porcine circovirus 1 (PCV1) in March, which resulted in an advisory to clinicians to stop using the vaccine. Subsequently, DNA from PCV1 and PCV2 was discovered in the RotaTeq vaccine. The FDA now says that there is no evidence that PCV causes illness or infection in humans while the benefits of the vaccine are substantial. ■

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

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- make informed, evidence-based recommendations about the usefulness and efficacy of integrative therapies to patients in their practice; and
- critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in integrative medicine as published in the scientific literature.

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Valerie Loner
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