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INSIDE

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Should Vitamin D Measurement Be Routine in All Cardiovascular Disease Patients?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *Hypovitaminosis D was found to be highly prevalent in U.S. adults with CVD, particularly those with both coronary heart disease and heart failure.*

Source: Kim DH, et al. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008;102:1540-1544.

VITAMIN D DEFICIENCY OCCURS IN ONE-THIRD TO ONE-HALF OF otherwise healthy middle-aged and elderly adults in the United States and worldwide. There is a growing body of evidence that hypovitaminosis D is highly prevalent in patients with various cardiovascular diseases (CVDs)[1-4] and, in fact, it may actually play a role in the pathogenesis of these illnesses.[5-9] Inadequate exposure to sunlight and/or inadequate vitamin D intake will result in abnormally low serum vitamin D levels, which have been found to be associated with cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, and dyslipidemia;[10,11] however, it must be recognized that many of these observations were from the results of relatively small studies.

Because the degree of occurrence of hypovitaminosis D in adults in the United States with a diagnosis of CVD was largely unknown, Kim and his colleagues examined its prevalence in U.S. adults with CVDs using data from the National Health and Nutrition Examination Surveys (NHANES) from 2001 to 2004.[12] Hypovitaminosis D was found to be present in 74% of the 8351 adults who had 25-hydroxyvitamin D (25-OH D) blood levels measured. Among CVD patients, it was more common in blacks than it was in Hispanic or

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Caucasian patients and it did not differ by gender. However, although it was found to be present in 68% of persons at low risk for CVDs, it was more prevalent in high-risk patients (75%), in patients with coronary heart disease (77%), and in subjects with both coronary heart disease and heart failure (89%) after controlling for age, race, and gender.

■ COMMENTARY

Several lines of evidence have suggested that hypovitaminosis D may contribute to CVDs by stimulating renin expression,[13] proliferation of cardiomyocytes[14] and smooth muscle cells,[15] and by producing secondary hyperparathyroidism[16] and inflammation.[17] Although the higher prevalence of hypovitaminosis D in patients with coronary heart disease and heart failure may have been caused by limited physical activity and sunlight exposure, studies have demonstrated that patients with heart failure compared to healthy controls differed in their lifestyle factors even in their earlier years, suggesting that hypovitaminosis D may occur earlier in life and precede the onset of CVDs.[18]

In conclusion, the Kim observational study revealed that hypovitaminosis D was highly prevalent in U.S. adults with CVDs, particularly those with both coronary heart disease and heart failure.[12] In addition, the study results raise the clinical possibility that treatment of vitamin D deficiency with vitamin D supplements and/or lifestyle measures might be able to reduce the frequency of CVDs; however, it must be clearly recognized that treatment strategies suggested by observational data are not always supported by randomized trials. Despite the positive results in small clinical trials in which vitamin D supplementation has promoted reductions in blood pressure,[19,20] left ventricular hypertrophy[21] and inflammatory cytokines,[22] vitamin D supplementation was not associated with a reduction in cardiovascular events in the Woman's Health Initiative,[23] although it should be noted that that particular trial was not designed to evaluate cardiovascular risk.[24] Obviously, although well conducted, randomized, double-blind clinical studies are needed to conclusively determine whether correction of vitamin D deficiency is able to contribute to the prevention and treatment of CVDs, at the present time there seems to be little risk for clinicians to recommend at least 800 IU of vitamin D daily for their adult (and especially elderly) patients and to consider prescribing even higher doses of vitamin D if needed to correct persistently abnormally low vitamin D blood levels, especially for those patients whose lifestyle and/or illnesses prevent them from being outdoors. ■

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Asleep at the Wheel

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant for Cephalon and Ventus, and serves on the speaker's bureaus for Cephalon and Boehringer Ingelheim.

Synopsis: *Use of the benzodiazepine-like hypnotics (z-hypnotics), zolpidem and zopiclone, is associated with an increased risk of crash, particularly in young people.*

Source: Gustavsen I, et al. Road traffic accident risk related to prescriptions of the hypnotics, zolpidem, flunitrazepam and nitrazepam. *Sleep Med* 2008;9:818-822.

THIS REPORT ORIGINATED WITH THE NORWEGIAN INSTItute of Public Health. It is a 19-month, retrospective analysis of all (!) Norwegians aged 18-69 years. The authors collected data on prescription medications, road traffic accidents, and emigration/death. They evaluated accidents occurring within both a 1-week period and a 2-week period following dispensing of 4 specific sleeping pills: nitrazepam, flunitrazepam, zopiclone, and zolpidem. The first 2 agents, nitrazepam and flunitrazepam, are benzodiazepine hypnotics not available in the United States.

The database for this study was 3.1 million. The authors calculated standard incidence ratios (SIRs) for the risk of accident for exposed (e.g., filling a hypnotic prescription) and non-exposed people. Individuals who simultaneously filled prescriptions for other psychoactive drugs (e.g., opiates, benzodiazepines, z-hypnotics, or carisoprodol) were excluded from analysis.

Zopiclone was by far the most commonly prescribed hypnotic in this study. The number of crashes and the SIR for each of the studied agents is presented in the Table *(see page 28)*.

As can be seen from the Table, all 4 of the hypnotics were associated with an increased risk of crash, with statistically significantly increased SIRs. For zopiclone and zolpidem, the risk was slightly more than doubled. The highest SIRs were found in the youngest age groups for all hypnotics; in fact, the increased risk of crash for those who were taking hypnotics was not statistically significant for those older than age 55 years. Men tended to have higher SIRs for all agents than did women. Exclusion of those individuals who were taking other

Table
Crashes per study drug

Hypnotic	Zopiclone	Zolpidem	Nitrazepam	Flunitrazepam
Number of crashes	n = 129	n = 21	n = 27	n = 18
Standardized incidence rate for crashes	2.3	2.2	2.7	4.0

psychoactive drugs did not change the results, nor did evaluation of crash risk for 2 weeks after medication was dispensed compared with 1 week after the prescription was filled.

■ COMMENTARY

First of all, the term "accident" is out, and the term "crash" is in. Crash is now the term used by governmental agencies and public health organizations. Use of the word crash is believed to be more effective in describing the devastation of vehicular impact, and also to stigmatize vehicular mishaps. Many are not accidents, and could have been prevented by more responsible behavior by the driver(s) involved.

The relationship between sleep, sleep disorders (including insomnia), and crash is a complicated and frightening one. Inadequate sleep (e.g., from simply not dedicating enough time to sleep [self-imposed sleep deprivation]) and obstructive sleep apnea are well-documented causes of increased crash risk.[1-4]

The association between insomnia and car crash is less clear. In one published survey, people who experienced chronic insomnia had a 2-fold increased risk of automobile accidents compared to people who were fatigued for other reasons.[5] Importantly, that survey did not control for hypnotic use and was based on self-report.

The current report brings some clarity to the issue of insomnia and car crash risk, and suggests that the hypnotics used to treat insomnia may contribute to any increased risk of crash that is associated with sleeping difficulty. Benzodiazepines, which are known to be sedating and anxiolytic, are accepted as contributing to an increased risk of crash. It was hoped that the non-benzodiazepine hypnotics (the "z-hypnotics") would be able to induce safe sleep without this associated risk of crash. Based on the current report, that belief appears to be false. This current study documents an increased crash risk with the z-hypnotics, zolpidem and zaleplon, even after controlling for significant confounders. This increased risk may be independent of the "sleep driving" phenomenon[6] that has recently surfaced in relationship to use of the benzodiazepine-receptor hypnotics.

This is not a perfect study. For one thing, it appears not to have controlled for exposure, e.g., the fact that the more a person drives, the more likely he is to crash. While the report seems to suggest that hypnotics do not carry an increased risk for crash in older individuals, that finding may results from the fact that older people drive less.

What to tell patients? First, hypnotics are not the ideal choice for chronic insomnia. Second, patients need to be warned about the increased risk of crash and other mishaps while under the influence of these agents. They should be advised to take them only when they are ready for sleep and have 7 or more hours to devote to sleep.

And we should also advise them about the risk for drug interactions and increased crash risk related to the use of other drugs, including over-the-counter agents. For example, there is an increased vehicular crash risk with narcotic analgesic use and antihistamine use.[7] And we don't even know what increased risk the combinations of these agents (and others) brings! ■

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B_{12} and Canker Sores

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *Vitamin B_{12} was effective in the treatment of recurrent aphthous stomatitis.*

Source: Volkov I, et al. Effectiveness of vitamin B_{12} in treating recurrent aphthous stomatitis: A randomized, double-blind, placebo-controlled trial. *J Am Board Fam Med* 2009;22:9-16.

These researchers from the department of family Medicine at Ben-Gurion University in Israel previously reported the observation that treating patients with low serum levels of vitamin B_{12} also cleared their recurrent aphthous stomatitis (RAS).[1] In this randomized, double-blind, placebo-controlled trial, they set out to confirm their observation. They recruited 84 adult patients with RAS for at least 1 year from the practices of 20 family physicians. After excluding those with Behçet's disease, other inflammatory disorders, or HIV-AIDS; recent recipients of B_{12}; recent treatment of RAS by other means; known B_{12} deficiency; and other conditions, 58 patients remained. All patients had serum vitamin B_{12} levels at study entry. They were instructed in a method of recording severity of pain and filling out the "Aphthous Ulcers Diary." Patients were randomized to receive sublingual vitamin B_{12} 1000 mcg at bedtime or matching placebo. The intervention and control groups were similar in all respects. The patients were evenly divided between men and women. The average age was about 30 years. On average they had suffered from RAS for about 10 years. The intervention group was divided into those with an initial B_{12} level less than 250 pg/mL and those with a level greater than that. The two subgroups did not differ statistically. The trial lasted 6 months. During the first 4 months of the study both groups had reduction in the average number of days of duration for an RAS episode (from 11.0 to 5.7 for the intervention group and 8.7 to 4.5 for the control group). During the next two months the average number of days for the control group remained steady, but the B_{12} group had a further reduction to 2.0.

There was a similar pattern in the reduction of the average number of aphthous ulcers per month (from 27.6 to 14.0 for the intervention group and 21.5 to 13.0 for the control group). After that, the curves diverged dramatically, and at 6 months the intervention group averaged 3.9 ulcers per month vs 13.4 for the control group. The graph of average level of pain showed a non-significant separation at month 4, and further separation at months 5 and 6 that were significant. The results did not depend on the initial serum vitamin B_{12} level. No patient reported an adverse reaction.

■ COMMENTARY

Aphthous ulcers (commonly known as canker sores) are the most common inflammatory lesions of the mouth, occurring in up to 10% of the population with more women afflicted than men.[2] Their cause is unknown. They are associated with anemia, gastrointestinal disease such as Crohn's disease and ulcerative colitis, HIV infection, and Behçet's disease. Acidic, salty, and spicy foods can trigger an attack. Treatment is symptomatic with topical anesthetics. Topical tetracycline has been effective, as have sucralfate solution and topical steroids. For severe lesions, thalidomide, antimetabolites, and immunomodulating agents have all been employed.[3] The association of aphthous ulcers and vitamin B_{12} deficiency has been recognized for many years.[4-6] What set this study apart is that the majority of patients were not B_{12}-deficient.

As you digest the findings of this study, there are some things you should consider: 1) These patients had severe ulcerative disease (I can't think of any patients that I've treated that had that many ulcers per month); 2) This was a small study—there weren't enough subjects to identify harm; 3) The investigators' method of recruitment (advertising to local family physicians) may have biased their study to patients with more severe disease. The study also raises a question: Why did both groups show improvement in the first 4 months? Despite my comment about low number of subjects, you should also consider that vitamin B_{12} is infrequently associated with adverse side effects, and it's cheap. If you have a patient who fits the profile of patients in this study, vitamin B_{12} may be the answer. ■

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Pharmacology Update

Milnacipran HCl Tablets (Savella™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

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Drs. Chan and Elliott report no financial relationship to this field of study.

THE FDA HAS APPROVED ANOTHER SELECTIVE SEROtonin and norepinephrine reuptake inhibitor for the management of fibromyalgia (FM). Milnacipran is more selective for norepinephrine than serotonin. This is in contrast to venlafaxine, which is more selective for serotonin and duloxetine, which is balanced in inhibition. Milnacipran is licensed from Pierre Fabre Medicament and Cypress Biosciences, Inc., and marketed by Forest Pharmaceutical, Inc., as Savella™.

Indication

Milnacipran is indicated for the management of fibromyalgia.[1]

Dosage

The recommended dose is 100 mg daily (50 mg twice daily). Dose escalation should be over 7 days using the following schedule: 12.5 mg (day 1), 12.5 mg twice daily (days 2-3), 25 mg twice daily (days 4-7), and 50 mg twice daily (after day 7). It may be increased to 200 mg daily based on response and tolerability.[1] Maintenance dose should be reduced to 25 mg twice daily for patients with severe renal impairment. No dose adjustment is necessary for patients with mild-to-moderate hepatic impairment or mild renal impairment. The drug should be used with caution in patients with moderate renal impairment and severe hepatic impairment.

Milnacipran is available as 12.5 mg, 25 mg, 50 mg, and 100 mg tablets.

Potential Advantages

Milnacipran-treated patients showed improvement in pain and overall improvement in FM compared to placebo.[1-3] The drug does not appear to have any clinically significant pharmacokinetic drug-drug interactions.[1]

Potential Disadvantages

Milnacipran does not appear to improve quality or quantity of sleep. The most common adverse effects of milnacipran compared to placebo were nausea (37% vs 20%), headache (18% vs 14%), constipation (16% vs 4%), hot flush (12% vs 2%), insomnia (12% vs 10%), dizziness (10% vs 6%), hyperhidrosis (9% vs 2%), and vomiting (7% vs 2%). Milnacipran shares the same class warning for suicidality as other selective serotonin and norepinephrine reuptake inhibitor antidepressants. Overall improvement seems to lessen with longer duration of therapy (i.e., 15 vs 27 weeks).

Comments

The approval of milnacipran was based on two pivotal U.S. Phase III clinical trials involving predominately female patients (~95%) with a mean age of 50 years.[2-4] One study (study 1) was 27 weeks in duration (n = 888) and the other (study 2) was a 15 weeks (n = 1196). Patients met American College of Rheumatology criteria for fibromyalgia. These included a history of widespread pain for 3 months and pain present at 11 or more of the 18 tender point sites. The minimum mean baseline pain score was ≥ 50 mm on a 100 visual analog scale (VAS) compared to ≥ 40 for study 2. Subjects were randomized to milnacipran 100 mg, 200 mg, or placebo at a 1:1:2 ratio in study 1 and 1:1:1 in study 2. Each study included a 3-week dose-escalation period and 12 weeks or 24 weeks of a stable dose. The primary efficacy outcome for FM was a composite criterion involving pain, patient global impression of change, and physical function. Patients were categorized as responders to therapy if they had a ≥ 30 improvement from baseline on VAS score, a rating of much improved or very much improved on Patient Global Impression of Change (PGIC), and a ≥ 6 point improvement in the SF-36 Physical Component Summary from baseline. FM pain outcomes included the first 2 criteria. Analysis of the results were based on baseline observation carried forward (BOCF) for the 15-week study and a modified BOCF for the 27-week study. Based on this approach, all subjects who missed the last assessment (week 15) were considered non-responders. For the 27-week study, BOCF was applied to subjects who dropped out of the study before week 15 and last observation carried forward (LOCF) for subjects completing week 15. At 15 weeks, composite response rates were 19.6% for 100

mg, 19.3% for 200 mg, and 12.1% for placebo in study 1, and 15.4%, 14.6%, and 9.2%, respectively, for study 2. These all reached statistical significance. At 27 weeks the FM composite responder rates were not statistically significant. The FM pain composite responder rates were statistically significant for both doses of milnacipran at 15 weeks. The rates were 27.2%, 26.8%, and 19.3% for study 1, and 23.8%, 26.2%, and 16.9% for study 2. At 27 weeks only the 200 mg dose reached statistical significance, likely due to a larger sample size and statistical power. Pain relief was detected after week 1 and maximal relief after week 9. Subjects reported greater overall improvement in terms of FM based on patient global assessment at week 15 for both doses but only for the 200 mg dose at week 27. In the two clinical trials, approximately one-quarter of subjects discontinued participation due to adverse events.

Clinical Implications

Milnacipran is the most recent drug approved for FM. Pregabalin and duloxetine also have FDA approval, while tricyclic antidepressants, SSRIs, and gabapentin have been both studied and used in clinical practice. Without comparative studies, the relative effectiveness of milnacipran vs other agents is not known. Recently published systematic reviews make a strong case for TCAs such as amitriptyline.[4,5] The magnitude of effect for pain reduction was considered large for TCAs and small for SNRIs (duloxetine and milnacipran).[4] In addition, TCAs reduced fatigue and sleep disturbance, while milnacipran improved fatigue but not sleep quality or quantity. ■

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CME Questions

9. Hypovitaminosis D:
a. was more common in Caucasian patients than in black or Hispanic patients.
b. was found to be present in only 35% of persons at low risk for CVDs.
c. was found to be present in 89% of patients with both coronary heart disease and heart failure.
d. need not be treated in patients older than age 85 years.

10. Sleeping pill use and increased risk of car crash:
a. occurs with benzodiazepine agents, but not with the benzodiazepine-like hypnotics (z-hypnotics).
b. occurs both with benzodiazepine and with benzodiazepine-like hypnotics (z-hypnotics).
c. is greater for older than for younger people.
d. is greater for women than for men.

11. In the study of recurrent aphthous stomatitis, sublingual vitamin B_{12} was associated with:
a. a reduction in pain.
b. a reduction in episode duration.
c. a reduction in the number of lesions per month.
d. All of the above

Answers: 9. c, 10. b, 11. d.

CME Objectives

The objectives of *Internal Medicine Alert* are:
- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Simplifying Dosing for Actinic Keratoses

Source: Zeichner JA, et al. Placebo-controlled, double-blind, randomized pilot study of imiquimod 5% cream applied once per week for 6 months for the treatment of actinic keratoses. *J Am Acad Dermatol* 2009;60:59-62.

ACTINIC KERATOSES (AK) ARE—AT best—precancerous skin lesions, and at worst (a belief held by many leaders in the skin cancer field), skin carcinoma in situ. In either case, the combination of cosmetic burden, troublesome symptoms, and association with squamous cell cancer motivates their destruction. Although it is commonplace to utilize simple local destructive measures (e.g., cryotherapy) to destroy an individual lesion, it is becoming increasingly clear that field therapy (i.e., treating an entire region to include both evident and subclinical AK lesions) provides a better and more lasting service to the patient.

Imiquimod is an immune system upregulator that has shown excellent efficacy in eradication of AK. As with all other topical agents employed for this purpose, local adverse effects and complexity of dosing regimen are limitations for some patients. Typical dose regimens for imiquimod rely upon 2-3 times weekly application of 5% cream for 8-16 weeks. Less frequent dosing, if effective, would reduce cost, enhance compliance, and possibly be better tolerated.

In this small study (n = 20), subjects applied imiquimod 5% cream once weekly for 16 weeks to half of the face, and placebo to the other half. At 16 weeks, 47% of imiquimod recipients showed marked improvement or better. In contrast to 2-3 times weekly dosing regimens, local adverse effects were essentially absent.

Total clearance rates with more frequent dosing are much higher, but so are intolerance and adverse effect rates. The authors suggest that these favorable results should be stimulus for larger, longer-duration studies. ■

Aerobic and Resistance Training Effects in PAD

Source: McDermott MM, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: A randomized controlled trial. *JAMA* 2009;301:165-174.

THE PRESENCE OF PERIPHERAL ARTERIal disease (PAD), confirmed by an ankle-brachial index of < 0.95, is often manifest by limitation in ability to walk, pain with walking, and limitation in performance of normal daily activities. For most patients, smoking cessation is the most important intervention. Pharmacotherapy is of limited value. Exercise training has been suggested as a method to improve oxygen utilization by the tissues and functional ability.

McDermott et al studied PAD patients (n = 156) who were randomized to aerobic training (treadmill), resistance training (weight training), or control. The treadmill group exercised 3 times weekly, beginning at a 2 mph walking speed for 15 minutes, working up to 40 minutes (with increases in speed and grade as tolerated). The resistance training group exercised 3 times weekly with knee extensions, leg presses, and leg curls. Both groups were followed for 6 months. The primary outcome was distance on the 6-minute walk.

Treadmill exercise improved the primary endpoint, but the control and resistance training groups did not significantly differ. Treadmill exercise also improved distant vascular health, as demonstrated by improvements in brachial artery flow-mediated dilation (no improvement was seen in the control or resistance training groups). ■

Risks Associated with Morning BP Surge

Source: Kario K, White WB. Early morning hypertension: What does it contribute to overall cardiovascular risk assessment? *J Am Soc Hypertens* 2008;2:397-402.

AMBULATORY MONITORING OF BLOOD pressure (BP) has demonstrated a pattern of BP change typified by an overnight reduction in BP of 10-20% and a "morning surge" in BP beginning closely around the time of awakening. Even in patients with hypertension, morning surge in BP is seen. And it's not only BP that surges in the morning: Blood coagulability, plaque vulnerability, platelet aggregability, and blood viscosity also increase at this time. Because CV events (MI, stroke, arrhythmia) also cluster disproportionately around this circadian phenomenon, experts have opined that modulation of the morning BP surge might provide benefits in clinical outcomes.

The relationship between the morning BP surge and CV risk is strengthened by the observation that it correlates with arterial wall stiffness, left ventricular hypertrophy, and carotid intima-media thickness.

Office blood pressure is typically measured several hours after the morning surge. Encouraging more widespread use of at-home BP self-monitoring is a reasonable first step to obtain more information about morning BP. Since we have not yet learned which, if any, antihypertensives might hold special benefits on morning BP, and we do not have a major clinical trial confirming risk reduction through morning BP control, we lack sufficient evidence to mandate control of morning BP surge as a specific entity at this time. ■