INTERNAL MEDICINE ALERT

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INSIDE

Financial Disclosure: *Internal Medicine Alert's* editor, Stephen Brunton, MD, serves on the advisory board for Lilly, Boehringer Ingelheim, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Lilly, Kowa, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Might That Medrol Dosepak Trigger a Suicide?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Dr. Scherger reports no financial relationships relevant to this field of study.

Synopsis: *Adults treated with glucocorticoids in a primary care setting have a five-fold increase in suicide or suicidal behavior and other severe neuropsychiatric disorders. The risk is highest with first-time use of these medications.*

Source: Fardet L, et al. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. *Am J Psychiatry* 2012;169:491-497.

In this cohort study from the United Kingdom, Fardet et al reviewed medical records from 424 general practices from 1990 until 2008 for incidence rates of neuropsychiatric disorders following glucocorticoid therapy. There were 786,868 courses of oral glucocorticoids prescribed for 372,696 patients. The medications included prednisolone, prednisone, dexamethasone, triamcinolone, betamethasone, methylprednisolone, and deflazacort, all given orally. Neuropsychiatric disorders identified included depression, mania, delirium, panic disorder, and suicidal behavior.

A neuropsychiatric disorder was considered to be associated with the use of glucocorticoids if it occurred after initiating therapy and the patient did not have that diagnosis within the preceding 6 months. The treatment group was compared with two other groups: a random sample of other patients who did not receive glucocorticoids, and a random sample of others with the same underlying neuropsychiatric conditions who did not receive glucocorticoids.

Among the groups, matching was done within the same practice and stratified by age and sex. Adjustments were made for potential confounding variables including age, sex, past history of glucocorticoid use, past history of any neuropsychiatric disorder, daily dose of glucocorticoids, and underlying medical disease.

VOLUME 34 • NUMBER 15 • AUGUST 15, 2012 • PAGES 113-120

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The incidence rate for any neuropsychiatric disorder in the treatment group was 16 per 100 person years overall. The incidence rate was 22 for the first course of corticosteroid, 14 for the second course, and 12 for the third and later courses. The risk of suicide or suicide attempt was increased approximately five-fold (hazard ratio [HR] = 5.3; 95% confidence interval, 3.8-7.3) and was more likely in younger patients. The increase in risk by individual disorder was most marked for delirium (HR = 6.4; 5.9-6.8) and mania (HR = 5.7; 5.1-6.6), especially in older men. Other significant increases were shown for depression and panic disorder. Larger daily doses and prior history of neuropsychiatric disorders were associated with a greater risk for all of these outcomes.

The authors conclude that glucocorticoids increase the risk of suicidal behavior and neuropsychiatric disorders. Educating patients and their families about these adverse events and increasing primary care physicians' awareness about their occurrence should facilitate early monitoring.

■ COMMENTARY

Every time I give a short course of glucocorticoids in my practice — something I do not do as often as other physicians in my area — I hope that I am not causing an asceptic necrosis of the hip. I fear this because I have seen it in my practice. We are all aware that some patients given these steroids have mental health side effects. This study is a wake-up call that these mental health side effects may be serious and life-threatening in some patients.

Every time we prescribe a medication, a risk-benefit calculation takes place in our reflection. Large epidemiologic studies like this may help us avoid a disaster that otherwise is only likely to occur once in our practice lifetime. ■

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin.
MANAGING EDITOR: Neill L. Kimball.
SENIOR VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.

GST Registration Number: R128870672.

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

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

Back Issues: $21. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Does Aortic Valve Calcification Predict Cardiovascular Events?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

Synopsis: *The presence of aortic valve calcification (AVC) predicts cardiovascular and coronary event risk independent of traditional risk factors and inflammatory biomarkers, likely due to the strong correlation between AVC and subclinical atherosclerosis.*

Source: Owens DS, et al. Aortic valve calcium independently predicts coronary and cardiovascular events in a primary prevention population. *J Am Coll Cardiol Img* 2012;5:619-625.

Calcific aortic valve disease (CAVD) is common in older adults with an estimated prevalence of 25% in individuals older than 65 years of age.[1] It is caused by biological processes that share both epidemiological[2,3] and histopathological[4] similarities to coronary atherosclerosis.

The presence of aortic valve calcification (AVC) without obstruction has been found to be associated with a 50% increase in the risk of cardiovascular events.[5] Owens and his colleagues sought to determine whether the presence of aortic valve calcium detected on computed tomography (CT) scans predicts cardiovascular events in a younger cohort by performing a prospective analysis[6] of the subjects in the Multi-Ethnic Study of Atherosclerosis (MESA).[7] In the MESA study, all subjects who were 45 to 84 years old and free of clinical cardiovascular disease at baseline underwent CT for evaluation of AVC and coronary artery calcium (CAC) scoring. AVC was found to predict cardiovascular and coronary event risk independent of traditional risk factors and inflammatory biomarkers, likely due to the strong correlation between AVC and subclinical atherosclerosis.

■ COMMENTARY

The MESA study is a National Heart, Lung, and Blood Institute-sponsored, population-based investigation of

subclinical cardiovascular disease and its progression.[7] In addition to a comprehensive baseline examination including a clinic visit, baseline testing, evaluation of cardiovascular risk factors, and blood analyses, baseline CT scans were obtained and analyzed for both coronary artery and aortic valve calcium content. The aortic valve was considered to be calcified if calcific lesions resided solely within the aortic valve leaflets (i.e., exclusive of the aortic annulus and/or coronary arteries) and found to contain at least three contiguous pixels ≥ 130 Hounsfield units of brightness. Participants with baseline AVC had a higher prevalence of CAC compared to those subjects without AVC (87.1% vs 45.1%) with skewing of the distribution of CAC scores toward those subjects with more severe CAC.

CAVD appears to begin in midlife as a clinically latent but progressive disorder that is detected most often incidentally, following the performance of routine CT examinations. Even in this latent preobstructive phase, the presence of AVC appears to be a marker of increased cardiovascular risk. Echocardiographically detected aortic sclerosis in adults over the age of 65 has previously been demonstrated to be associated with a 50% increased risk of cardiovascular mortality and a 42% increased risk of myocardial infarction.[5] The results of this study appear to extend these previously reported findings into a younger, healthier, multiethnic population group and seem to offer at least a partial explanation for the observed association between aortic calcification and coronary events.

In summary, AVC appears to be an independent predictor of cardiovascular mortality after adjustment for traditional risk factors and CAC severity, even though the presence of CAC may be unrelated to progressive valve disease. These risk associations were attenuated after adjustment for CAC, but not for inflammatory markers, suggesting that AVC may actually be a marker of subclinical atherosclerosis severity. Even after adjustment for any risk factors that may be present, such as inflammation and/or subclinical atherosclerosis, it remains unclear how determination of AVC adds to cardiovascular risk prediction in a predictably significant way. In any case, clinicians should be aware that this easily determined marker may eventually prove to be very helpful to them in both primary and secondary cardiovascular disease prevention. ■

References

1. Stewart BF, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997;29:630-634.
2. Agmon Y, et al. Aortic valve sclerosis and aortic atherosclerosis: Different manifestations of the same disease? Insights from a population-based study. *J Am Coll Cardiol* 2001;38:827-834.
3. Owens DS, et al. Incidence and progression of aortic valve calcium in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Cardiol* 2010;105:701-708.
4. O'Brien KD. Pathogenesis of calcific aortic valve disease: A disease process comes of age (and a good deal more). *Arterioscler Thromb Vasc Biol* 2006;26:1721-1728.
5. Otto CM, et al. Association of aortic valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999;341:142-147.
6. Owens DS, et al. Aortic valve calcium independently predicts coronary and cardiovascular events in a primary prevention population. *J Am Coll Cardiol Img* 2012;5:619-625.
7. Bild DE, et al. Multi-ethnic study of atherosclerosis: Objectives and design. *Am J Epidemiol* 2002;156:871-881.

Studying the Issue of Off-label Prescribing in Primary Care

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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Dr. Gupta reports no financial relationships relevant to this field of study.

Synopsis: *Off-label prescribing is common in primary care and most of the time lacks the scientific evidence to support it.*

Source: Eguale T, et al. Drug, patient, and physician characteristics associated with off-label prescribing in primary care. *Arch Intern Med* 2012;172:781-788.

Simply put, off-label prescribing can be defined as the prescribing of a drug or medical device outside its licensed indication to treat a condition or disease for which it has not specifically received regulatory approval. For prescription drugs, the Food and Drug Administration (FDA) approval process is a complex one that requires submission of substantial evidence of efficacy and safety for specific clinical conditions. In the United States, based on the principle that the physician should partner with the patient to make the best treatment decision possible, it is legal for physicians to prescribe off-label drugs. Omission from the approved label does not mean that the FDA disapproves of an off-label use, it simply indicates that the

agency has not reviewed that specific use.

Unlike the use of drugs prescribed for FDA-approved indications, off-label uses may lack rigorous scientific scrutiny. In 2001, a study demonstrated that off-label prescribing accounted for 21% of overall use for 160 commonly prescribed drugs in the United States.[1] Off-label use was most common among cardiac and anticonvulsant medications and most off-label drug use had little or no scientific support. When an off-label use lacks such scientific basis, the potential for harm is the greatest. However, the risks and benefits of off-label prescribing have not been meticulously studied. As more and more physicians begin to use electronic health records (EHR), meeting the meaningful use requirement, including e-prescribing, and before having to provide an indication for each drug prescribed will become the norm, rather than the exception. Therefore, it is important that we understand the particular drug, patient, and physician characteristics associated with off-label prescribing in primary care.

In their study, Eguale et al used an EHR system to obtain prescription data from 113 primary care physicians in Quebec, Canada, from January 2005 to December 2009. A total of 253,347 electronic prescriptions for 50,823 patients were written during this period and treatment indication entry for prescriptions was mandatory. Any indication that could not be matched to the labeled therapeutic indication reported in the drug's package insert was considered off-label. Additionally, for each off-label use, methodology was used to determine whether there is strong scientific evidence for the off-label use of a drug for a particular treatment indication.

The researchers found that 11% of all prescriptions were prescribed for off-label indications and the results showed that 79% of off-label use lacked strong scientific evidence. Further, they discovered that the highest percentage of off-label prescriptions were for central nervous system medications (26.3%), with 17.1% for anti-infective agents followed by 15.2% for ear, nose, and throat medications. Among central nervous system medications, the highest proportions of off-label use were for anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%). Additionally, among specific drugs with the highest off-label use were quinine sulfate (99.5% of total prescriptions), followed by gabapentin (99.2%), clonazepam (96.2%), amitriptyline (93.7%), trazodone (92.6%), and betahistine (91.5%). Medications with three or four approved indications were associated with lower off-label use compared to those with one or two approved indications. Sicker patients had lower off-label use than their counterparts. Medications approved after 1995 were also associated with lower off-label use than those approved before 1981. Physicians with high scores on evidence-based practice were less likely to prescribe off-label.

■ COMMENTARY

Like many things in life, there is no simple answer to the issue of off-label prescribing. In an ideal world, all uses of a prescription drug would be well analyzed and found to be safe and effective. However, in reality, when a physician writes a prescription, patients often assume that the drug has been tested and approved for the specific use by the FDA. While reasonable, that assumption does not hold true in one in every five prescriptions written in the United States. Such off-label use is both legal and often beneficial. Examples include the common use of some of the beta-blockers for performance anxiety and anticonvulsants for migraine prophylaxis. However, sometimes this type of use in the absence of rigorous scientific data can cause significant harm, as exemplified by drugs such as Fen-Phen, which led to cardiac valve damage in patients. So, the idea is neither to reject nor to encourage the use of off-label prescribing but rather to understand the process better in order for physicians to effectively use it.

It is important to note that there is a significant gap between what approved/indicated drugs are available and the needs of the primary care physician in a busy practice. While there is no doubt that with the implementation of health reform and EHR the scrutiny will increase over the proper utilization of health resources, including off-label prescribing, it would be a mistake to attempt to eliminate it. Patients do benefit from off-label prescribing that is supported by sound scientific and medical evidence. Physicians' autonomy to prescribe drugs off-label carries important advantages. It recognizes that clinical practice has many more challenges than can be classified into drug categories, and innovation at the clinical level allows discovery as well. However, gaps in clinical innovations and data scrutiny must be filled by an aggressive clinical effectiveness research agenda that focuses on the scientific support for drug indications that may not necessarily be FDA approved. The current study by Eguale et al attempts to initiate this process by better understanding the various characteristics associated with off-label prescribing. As EHRs are implemented, it may be wise for the Centers for Medicare & Medicaid Services to consider systematically collecting post-marketing data to quantify harms and benefits of common off-label drug uses to develop evidence for their use on a case-by-case basis as may be appropriate. This will help to better guide physicians' clinical decisions as to where it is most appropriate to use off-label drugs vs scenarios that compromise patient safety and/or represent wasteful use. ■

Reference

1. Radley DC, et al. Off-label prescribing among office-based physicians. *Arch Intern Med* 2006;166:1021-1026.

Phentermine/Topiramate Extended-Release Capsules (Qsymia™ CIV)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

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

THE FDA HAS APPROVED A SECOND WEIGHT-LOSS DRUG WITHIN the last month. This product is a combination of phentermine, an anorectic, and the antiepileptic topiramate. Phentermine/topiramate (PHEN/TPM) is manufactured by Catalent Pharma Solutions and marketed by Vivus Inc. as Qsymia.

Indications

PHEN/TPM is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults.[1] PHEN/TPM is for adults who are obese (≥ 30 kg/m^2) or overweight (≥ 27 kg/m^2) with at least one comorbidity such as diabetes, hypertension, or dyslipidemia.

Dosage

The recommended starting dose is 3.75 mg of PHEN and 23 mg of TPM daily for 14 days, after which it may be increased to 7.5 mg/46 mg daily. If a 3% weight loss has not been achieved after 12 weeks, treatment may be discontinued or the dose may be increased further to 15 mg/92 mg after 12 weeks. If a 5% weight loss is not achieved after 12 weeks of treatment with 15 mg/92 mg, treatment should be discontinued. In patients with severe renal dysfunction or moderate hepatic dysfunction, the dose should not exceed 7.5 mg/46 mg. Discontinuation of treatment should be done gradually to avoid possible seizures.[1]

PHEN/TPM is available as 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg capsules.

Potential Advantages

PHEN/TPM provides another alternative with a different mechanism of action for weight loss in obese and overweight patients.

Potential Disadvantages

Topiramate may increase the risk of suicidal thoughts and behavior, mood disorders, cognitive impairment, kidney stones, oligohidrosis, and hyperthermia.[1]

Comments

The efficacy of PHEN/TPM was evaluated in two randomized, double-blind, placebo-controlled studies of 56 weeks duration.[1-3] Study 1 (EQUIP) enrolled obese subjects and study 2 (CONQUER) enrolled obese and overweight subjects with two or more significant comorbidities. Both studies had a 4-week titration period and a 56-week treatment period. Subjects in EQUIP were randomized at a ratio of 2:1:2 to placebo (n = 514), PHEN/TPM 3.75 mg/23 mg (low dose; n = 241), and 15 mg/92 mg (n = 512). Subjects in CONQUER were randomized at the same ratio to placebo (n = 994), PHEN/TPM 7.5 mg/46 mg (mid-dose; n = 498), and 15 mg/92 mg (top dose; n = 995). Efficacy endpoints were percent of weight loss from baseline to week 56 and percent achieving at least 5% loss of body weight. The secondary endpoint was percent of subjects achieving at least 10% loss of body weight. Analysis was based on intent-to-treat and last observation carried forward. In EQUIP, the percent mean difference in placebo-adjusted weight loss (95% CI) was 3.5% 92.4-4.7) for 3.75 mg/23 mg and 9.4% (8.4-10.3) for the 15 mg/92 mg. The percentage of patients (placebo subtracted [95% CI]) losing ≥ 5% body weight was 27.6% (20.4-34.8) and 49.4% (44.1-54.7), respectively. For a 10% weight loss, the values were 11.4% and 39.8%. For CONQUER, placebo-subtracted mean changes from baseline were 6.6% for 7.5 mg/46 mg and 8.6% for 15 mg/92 mg. Values for the 5% and 10% weight loss were 41.3% and 49.2%, and 29.9% and 40.3%, respectively. PHEN/TPM modestly improved cardiovascular, metabolic, and anthropometric risk factors (e.g., blood pressure, lipid profile, and waist circumference) in a dose-dependent manner with waist circumference being the most significantly affected. The placebo subtracted differences for the three strengths were -2.5, -5.2, and -6.8/-7.8.[1]

In a small similarly designed study (n = 130), obese type 2 diabetic subjects were randomized to placebo or top dose of PHEN/TPM.[4] Mean weight loss was 9.4% for PHEN/TPM and 2.7% for placebo. Percent with 5% or greater weight loss was 49% and 13%, respectively. Change in HbA1c was 1.6% and 1.1% (P = 0.38). The most common adverse events mid-dose vs placebo were dry mouth (13.5% vs 2.8%), paresthesia (13.7% vs 1.9%), constipation (15.1% vs 6.1%), elevation of serum creatinine ≥ 0.3 mg/dL (7.2% vs 2.0%), and dysgeusia (7.4% vs 1%).

Clinical Implications

PHEN/TPM is the second recent addition for the pharmacologic management of obesity after lorcaserin. The

magnitude of benefit appears similar between the lowest dose of PHEN/TPM and lorcaserin. The FDA Guidance for Industry: Developing Products for Weight Management indicates that the primary efficacy endpoint should show a statistical difference of 5%, or at least 35%, and approximately double the proportion of subjects in the drug group should achieve a loss of 5% or greater in baseline body weight compared to the control group.[5] Both lorcaserin and low-dose PHEN/TPM did not reach the efficacy benchmark of a statistical difference of 5% in mean weight loss between drug and placebo. The mid and top doses of PHEN/TPM did meet this benchmark as provided in the FDA guidance. ■

References

1. Qsymia™ Prescribing Information. Mountain View, CA: Vivus Inc.; July 2012.
2. Gadde KM, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): A randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:1341-1352.
3. Allison DB, et al. Controlled-release phentermine/topiramate in severely obese adults: A randomized controlled trial (EQUIP). *Obesity* 2012;20:330-342.
4. www.fda.gov/downloads/advisorycommittees/.../drugs/.../ucm218821.pdf. Accessed July 30, 2012.
5. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071612.pdf. Accessed July 30, 2012.

CME Objectives

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

CME Instructions

To earn credit for this activity, follow these instructions:

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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter! ■

CME Questions

1. **In the study by Eguale et al, the highest percentage of off-label prescriptions was for central nervous system medications. Which drug subgroup was prescribed off-label most commonly?**
   a. Anticonvulsants
   b. Anti-anxiety medications
   c. Antipsychotics
   d. Antidepressants

2. **Detection of aortic valve calcification on CT scanning:**
   a. is an interesting observation of little or minimal value.
   b. is of significant value in predicting cardiovascular and coronary event risk in all patients.
   c. is of clinical value only in patients with significantly abnormal traditional risk factors and/or abnormal inflammatory biomarkers.

3. **All of the following are neuropsychiatric disorders associated with the use of glucocorticoids *except*:**
   a. mania.
   b. depression.
   c. suicide.
   d. panic disorder.
   e. bipolar disorder.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Risk for Zoster from the Vaccine in Immunosuppressed Persons

Source: Zhang J, et al. *JAMA* 2012;308: 43-49.

The prevailing wisdom suggests that because herpes zoster vaccine (ZOS) is a live virus, it should not be administered to persons receiving immunosuppressive treatments, such as biologic agents or methotrexate for rheumatoid arthritis, or chronic prednisone therapy of 20 mg/d or more. The concern is that instead of mounting an immune response to the vaccine, vaccinees might actually experience a case of shingles as a result of the vaccine.

To examine the real-life risk of an acute zoster infection after ZOS, a retrospective analysis was performed on a large Medicare database (n = 463,541) of persons with a diagnosis of rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease. Any one of these disorders would be commonly treated with immunosuppressive agents, corticosteroids, or both.

The analysis looked at the number of cases of shingles within 42 days of ZOS, anticipating that if the live virus vaccine had induced shingles, it should certainly have happened within that 6-week window after vaccination.

No increased incidence of shingles was seen in ZOS recipients, even in patients on biologics. Indeed, ZOS was associated with a 39% lower risk of shingles during the 42-day window of observation, and a reduced risk during the subsequent 2 years (median) of follow-up. ZOS appears to be beneficial even in immunocompromised individuals, and the authors challenge the propriety of current recommendations that advise against ZOS administration in such populations. ■

Elucidating the 'Best' Interval for Bone Density Screening in Osteoporosis

Source: Yu EW, Finkelstein JS. *JAMA* 2012;307:2591-2592.

Once a baseline bone mineral density (BMD) has been obtained, it is unclear when the study should be repeated. For one thing, the literature suggests that only about 30% of bone strength may be attributable to bone density. Additionally, some of the interventional trials using bisphosphonates have found fracture reduction despite continuation of bone density *loss* over the first year or two of intervention. Finally, the rate at which BMD declines has been linked to the baseline BMD.

For instance, a study that looked at menopausal women (age > 67 years) for progression of BMD loss found some fairly startling results: It would take approximately 15 years for 10% of women with normal baseline BMD (T score < -1.5) to incur sufficient loss of BMD to cross the diagnostic threshold for osteoporosis (T score < -2.5). Similarly, for women with osteopenia (T score -1.5 to -2.0) at baseline, it would require 5 years for 10% of them to progress to frank osteoporosis. At the greatest level of osteopenia (T score -2.0 to -2.5), progression to osteoporosis in 10% of women would be expected to occur within 1 year. These projections assume no addition of new risk factors known to accelerate bone loss.

Although it is tempting to get BMD more often, it may not be helpful. Although the data are sufficiently uncertain that the USPSTF has been unable to provide confirmation of a preferred schedule, Yu et al suggest the following rescreening intervals for postmenopausal women: for women with normal BMD at baseline, 10 years; for women with mild osteopenia and low fracture (FRAX) score at baseline, 5-10 years; for women with moderate osteopenia or FRAX score approaching treatment threshold, 2 years. ■

Cerebral Aneurysms: What's in Your Patient's Future?

Source: UCAS Japan Investigators. *N Engl J Med* 2012;366:2474-2482.

The UCAS (unruptured cerebral aneurysm) Japan study began enrolling patients with incidentally discovered cerebral aneurysms (CRAs) for an observational study in 2001. The primary purpose of the study was to better delineate the natural history of incidentally discovered CRAs (as opposed to discovery through neurologic signs or symptoms). Prior to this trial, it had been generally recognized that CRAs < 7 mm rarely rupture, and that posterior circulation CRAs have a greater risk than anterior.

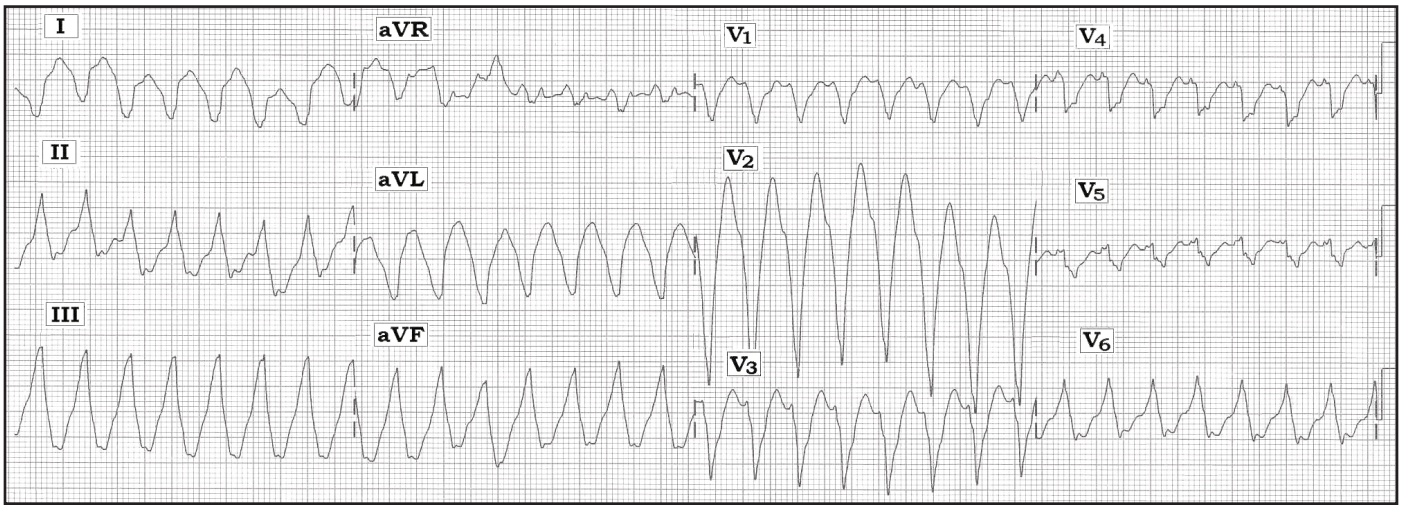
This prospective cohort study included patients (n = 6413) with incidentally discovered CRA and minimal, if any, disability. Subjects were followed for up to 8 years. During this interval, the annual rate of CRA rupture was approximately 1%. When rupture did occur, it was fatal in 35% of cases, or led to moderate-severe disability in another 29%.

The most important predictive factors for rupture were size of the CRA, age, and gender (females are at greater risk). For example, when compared with lesions < 7 mm, a 7-9 mm lesion had a three-fold increase of rupture, and a lesion > 10 mm had a nine-fold increased risk. Risk in women was 1½ times as great as men, and persons over age 70 were 21% more likely to experience aneurysm rupture. Because the entire population of enrollees was Japanese, the generalizability of these results may have limitations, but nonetheless provide perhaps the most accurate mapping of risk factors for rupture of CRAs. ■

Why is the Rhythm VT?

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.



Scenario: The ECG shown above was obtained from a patient whose blood pressure was dropping. How many reasons can you cite to support a diagnosis of ventricular tachycardia (VT)?

Interpretation: The 12-lead ECG in the Figure shows a regular wide complex tachycardia (WCT) rhythm at a rate of ~180/minute. Sinus P waves are absent. The rhythm is sustained VT and the patient is in need of immediate electrical therapy (synchronized cardioversion of defibrillation). Many reasons can be cited to support definitive diagnosis of sustained VT. These include:

1) Statistically, at least 80% of all *regular* WCT rhythms of uncertain etiology are VT. The likelihood of VT increases to *more than* 90% if the patient is middle-aged or older (especially if the patient has underlying heart disease).

2) Although on occasion regular WCT rhythms may be due to a supraventricular etiology with either preexisting bundle branch block or aberrant conduction — VT must *always* be assumed until proven otherwise, because it is a potentially life-threatening arrhythmia.

3) Extreme axis deviation is present. Mild-to-moderate left or right axis deviation may be seen with supraventricular rhythms. However, total negativity in either lead I or lead aVF suggests extreme axis deviation, and is virtually diagnostic of VT.

4) The QRS complex is both markedly widened (to over 0.16 second in many leads) — and the QRS is lacking in organized morphology (which we convey by describing the QRS as "ugly"). Both features are highly suggestive of VT. Aberrant conduction most often manifests a more organized QRS morphology that is consistent with some type of conduction defect (left or right bundle branch block with or without hemiblock).

5) There is ECG evidence of delayed initial ventricular activation. The presence of an r-to-S-nadir of more than 0.10 second in one or more precordial leads is highly suggestive of VT. This is best seen in lead V5.

6) Always assume VT until proven otherwise. Treat the patient accordingly.

For more information on this ECG Review, please visit: www.kg-ekgpress.com/acls_comments-_issue_11/. ■

In Future Issues:

Continuation with Statin Therapy and the Risk of Primary Cancer: A Population-Based Study

Elderly Women with Atrial Fibrillation at Greater Risk for Stroke

Tudorza Pressair for Treating Chronic Obstructive Pulmonary Disease

PHARMACOLOGY WATCH

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

FDA Approves First New Anti-Obesity Drug in Years

In this issue: Lorcaserin for weight loss; statins and fatigue; treatment-resistant gonorrhea; hydrocodone classification changes; USPSTF recommendations; and FDA actions.

Magic bullet for weight management?

The FDA has approved lorcaserin, the first new weight loss medication in more than a decade. The drug is approved for chronic weight management in adults with a body mass index of 30 or greater, or 27 or greater in those with weight-related conditions such as high blood pressure, type 2 diabetes, or hypercholesterolemia. Lorcaserin works by activating the serotonin 2C receptor in the brain, which promotes satiety. Approval was based on the results of three randomized, placebo-controlled trials of nearly 8000 obese and overweight patients with and without type 2 diabetes. All participants received lifestyle modification and reduced-calorie diets as well as exercise counseling. Lorcaserin was associated with an average weight loss of 3-3.7% compared to placebo over 1 year. Those with type 2 diabetes experienced favorable changes in glycemic control. There is no evidence of valvulopathy associated with the drug; although serotonin syndrome is a concern, especially when the locaserin is taken with an SSRI or some migraine drugs. The most common side effects include headache, dizziness, fatigue, nausea, dry mouth, and constipation as well as hypoglycemia in diabetic patients. Lorcaserin will be marketed by Arena Pharmaceuticals as Belviq. ■

Do statins cause fatigue?

Statins may be associated with fatigue and exertional intolerance, according to a small study from UC San Diego. Researchers randomized just over 1000 patients (692 men and 324 women) to simvastatin 20 mg (lipophilic statin), pravastatin 40 mg (hydrophilic statin), or placebo for 6 months. The outcomes were self-ratings of change in baseline in "energy" and "fatigue with exertion." Statin users were more likely to report worsening energy and fatigue compared to placebo ($P = 0.002$) Fatigue and exertional intolerance was worse with simvastatin compared to pravastatin (simvastatin, $P = 0.03$; pravastatin, $P = 0.01$). Women were more severely affected than men. The authors acknowledge that these findings are based on small numbers and findings are provisional. However, they also state that "this is the first randomized evidence of affirming unfavorable statin effects on energy and exertional fatigue." They further suggest that these effects "germane to quality of life, merit consideration when prescribing or contemplating use of statins, particularly in groups without expected morbidity/mortality benefit." (*Arch Intern Med* published online June 11, 2012. doi: 10.1001/archinternmed.2012.2171). The study also raises the potential issue of increased adverse effects of lipophilic statins such as simvastatin. The various risks and benefits of lipophilicity have been debated for years. It is clear that highly lipophilic statins, such as the now removed cerivastatin (Baycol), may have more muscle toxicity, and may have more CNS adverse effects as well. Of currently marketed statins, simvastatin is the most lipophilic, while pravastatin and rosuvastatin are the least. ■

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Call to action for resistant gonorrhea

The World Health Organization (WHO) is calling for urgent action to prevent the spread of "untreatable gonorrhea" around the world. The concern is based on reports from several countries, including Japan, United Kingdom, Australia, France, Sweden, and Norway, of gonorrhea that is resistant to cephalosporin antibiotics — the last remaining treatment option. According to WHO, more than 100 million people are infected with gonorrhea annually, and the world is faced with "dwindling treatment options." WHO is calling for greater vigilance on the correct use of antibiotics and more research into alternative treatment regimens for gonococcal infections. The agency also calls for increased monitoring and reporting of resistant strains as well as better prevention, diagnosis, and control of gonococcal infections. Single-dose treatment to assure adherence is also important as is the treatment of partners. WHO also stresses education and prevention, with special attention to high-risk groups such as sex workers and men who have sex with men. Cephalosporin-resistant gonorrhea has not been reported in the United States yet, but surveillance systems are in place. According to a recent CDC editorial in the *New England Journal of Medicine,* "It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense..." (*N Engl J Med* 2012; 366:485-487). ■

Changes on horizon for hydrocodone drugs

Could Vicodin soon be a Schedule II drug? The answer may be yes depending on congressional action this summer. The U.S. Senate recently passed The FDA Safety and Innovation Act (S 3187) with an amendment to classify all hydrocodone-containing products from Schedule III to Schedule II. The House of Representative's version of the bill did not contain similar language, and the proposal is under consideration for the final bill to be sent to the President for signature later this summer. Meanwhile, lawmakers in New York are moving forward with legislation that would make all hydrocodone-containing drugs Schedule II. If enacted, these laws would categorize hydrocodone containing drugs, such as Vicodin and Norco, in the same group with morphine, oxycodone, and methadone. Schedule II drugs cannot be phoned in, and patients are required to receive a new prescription for each refill. The proposed tightened regulations are in response to the explosion of prescription opioid abuse nationwide. Meanwhile, pharmacy groups, such as the American Pharmacists Association, are opposed to the legislation and are actively lobbying against it, arguing that it is unnecessarily restrictive to patients who legitimately need access to these drugs. ■

Vitamin D and calcium supplements

The U.S. Preventive Services Task Force (USPSTF) has now recommended that vitamin D and calcium supplements above the usual recommended daily allowances are of no benefit to help prevent bone fractures in healthy older women, and may actually cause harm. In a draft recommendation statement issued in early June, the USPSTF concluded that there is insufficient evidence to recommend vitamin D for prevention of cancer or combined vitamin D and calcium for the prevention of fractures in postmenopausal women or men. They further recommend against daily supplementation of more than 400 IU of vitamin D and 1000 mg of calcium carbonate. Older adults who are at risk for falls may continue to take vitamin D (www.uspreventiveserviestaskforce.org/draftrec3.htm). The draft recommendation was issued just after a study was published showing calcium plus vitamin D supplements appear to be associated with lower mortality in older individuals. In a large meta-analysis, patients receiving both calcium and vitamin D had a 9% reduction in mortality (hazard ratio, 0.91; 95% confidence interval, 0.84-0.98), although vitamin D alone did not affect mortality (*J Clin Endocrinol Metab* published online May 17, 2012, doi: 10.1210/jc.2011-3328). ■

FDA actions

The FDA has issued opinions on two oral novel anticoagulants. The agency turned down Janssen's application for approval of rivaroxaban (Xarelto) for the treatment of acute coronary syndrome, at least for now. The FDA did not release the reasons for the decision, but speculation is they want more information from the ATLAS-ACS trial. Rivaroxaban was approved last year for prevention of venous thromboembolism after hip or knee replacement surgery, and also for stroke prevention in patients with non-valvular atrial fibrillation (AF). The FDA also delayed the approval of apixaban (which would represent the third novel oral anticoagulant along with dabigatran and rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular AF. It had been widely speculated that the drug would be approved this spring, especially given that the FDA had granted a priority review for apixaban last November. The delay is similarly due to the need for additional information from the ARISTOTLE trial. Once approved apixaban will be marketed by Bristol-Myers Squibb as Eliquis. ■