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INSIDE

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Excessive Daytime Sleepiness in a General Population Sample: The Role of Sleep Apnea, Age, Obesity, Diabetes and Depression.

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speaker's bureau of Cephalon, Boehringer Ingelheim, Merck, ResMed, and GlaxoSmithKline and is a consultant for Boehringer Ingelheim, Wyeth-Ayerst, and ResMed.

Synopsis: *Complaints of sleepiness are common in those being treated for depression, in diabetics, in the obese, in smokers, and in those with sleep apnea.*

Source: Bixler EO, et al. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab*. 2005;90:4510-4515.

THIS REPORT COMES FROM AN ANALYSIS OF DATA FROM THE Penn State Cohort, which was assembled to investigate the age distribution of sleep apnea. A random sample of 16,583 people older than age 20 were interviewed by phone; a subset of 1741 of these individuals also underwent formal sleep testing (polysomnography) in a sleep center. The phone interview used a questionnaire that included basic demographic and self-reported health and sleep information. The presence of sleepiness was assessed by asking, "Do you feel drowsy or sleepy most of the day but manage to stay awake?" and "Do you have any irresistible sleep attacks during the day?" If respondents endorsed a moderate or severe rating on either of those questions, they were considered sleepy for purposes of this study. Depression was considered to be present if the subject was currently being treated for depression or endorsed suicidal thoughts or attempts. Diabetes was considered to be present if the participant had been diagnosed with diabetes by a physician, or in the subset who was studied in the sleep lab, or if fasting glucose was > 126. Sleep testing was done using standard techniques and definitions, and sleep apnea was consid-

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ered to be present if the Apnea plus Hypopnea Index (AHI) was 15 or more events per hour of sleep.

The mean age of this cohort was 46.5 ± 0.1 years, and mean BMI was 26.3 ± 0.04 Kg/m^2. In this population, 8.7% were sleepy, 13.0% diabetic, 13.3% depressed, and 4.4 % had sleep apnea. Men and women were equally sleepy in this cohort. There was a decline in reported sleepiness between the ages of 30 and 75 years, with increased sleepiness for those younger than 30 and older than 75 years. There was a marked increase in the prevalence of sleepiness for those with BMIs above 28 Kg/m^2. There were also strong associations between reported sleepiness and both diabetes and treatment for depression.

In the subset of those randomly chosen 1741 participants who had sleep studies, those who reported sleepiness were no more likely to have low sleep efficiency (time spent sleeping divided by total time in bed) than those who did not. There were no differences in the sleep structure or quality of sleep between the sleepy and nonsleepy groups except for more awakenings for the sleepy group. Also, 18.3% of those with sleep apnea were sleepy, and 10.7% of those without sleep apnea were sleepy. This difference was statistically significant.

There was no association between reported sleepiness and the use of medications used to treat allergies, hypertension, thyroid disease, or "cardiac conditions," but those who used antidepressants were much more likely to report sleepiness. Bixler et al state that the relationship between sleepiness and depression did not change when they statistically controlled for the use of antidepressants, and they assert, "This supports the role of depression as a major risk factor for EDS in the general population."

After multivariate analysis, being treated for depression emerged as the most important risk factor for reporting sleepiness, followed by BMI, age (older people are less sleepy, at least up until the age of 75), self-reported sleep duration, diabetes, smoking, and finally sleep apnea.

COMMENTARY

This study interested me because it addresses an issue I have to consider nearly every day: the sleepy patient who doesn't have sleep apnea. What else could it be? While sleep specialists talk a lot about narcolepsy and other arcane disorders, we know they are uncommon. In this study, depression (which is common) emerges as a powerful influence on sleep. We already know that depression is the single most important factor for insomnia,[1] but the current paper suggests that depression and its treatment are also risk factors for sleepiness. Lifestyle, of course, also emerged as important, with both obesity and cigarette smoking conferring greater risk of sleepiness than sleep apnea. A large body of literature[1,2] indicates that chronic illness is a risk factor for insomnia, which is often vaguely defined. In line with that literature, this study implicates diabetes as a risk for sleepiness.

Sometimes I worry that I haven't gone far enough to evaluate patients who are referred for sleepiness if their sleep studies are negative for sleep apnea. This paper is reassuring to the clinician, and somewhat demystifies sleepiness, demonstrating that the "usual suspects" of depression, obesity, smoking, and diabetes are important underlying causes. Sleep

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apnea is prevalent and deadly, and it is important to rule it out, since CPAP treatment is highly effective. But if a sleep study is negative for sleep apnea? This paper suggests that many sleepy folks with negative sleep studies could benefit from those things that we do every day: counseling about weight loss and smoking cessation, considering depression or metabolic illness, evaluation of medications, and reassurance. ■

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NSAIDs May Cause Urinary Retention

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

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

Synopsis: *A 3.3-fold increase in acute urinary retention was found in new male users of nonsteroidal anti-inflammatory drugs (NSAIDs) compared to non-users in a large primary care database from the Netherlands. The risk for all male NSAID users was 2.3-fold greater.*

Source: Verhamme KM, et al. Nonsteroidal anti-inflammatory drugs and increased risk of acute urinary retention. *Arch Intern Med.* 2005:165;1547-1551.

A SEARCH FOR ACUTE URINARY RETENTION FROM 1995-2002 in all men aged 45 years or older tracked in the Netherlands Integrated Primary Care Information Project for at least 6 months found 536 cases out of a source population of 72,000 men. The database contains information on 500,000 patients from 150 general practitioners in the Dutch health system which uses a gatekeeper approach for medical care. These cases were matched for age and date of the urinary retention diagnosis with 10 male controls from the same population who had no record of using the drugs studied.

Prescription records for all NSAIDs, COX-2 inhibitors, and aspirin were matched to cases and controls if they were received within 1 week prior to the date, or had been used within the prior 6 months.

The overall increased risk for acute urinary retention was 2.3 compared to non-users. For current users, the risk was highest at 3.3 when the prescription was new within the prior week, compared to 1.8 for long-term users. Past use alone was not associated with any risk. Medication doses less than the recommended average daily dose as defined by the World Health Organization were also not associated with increased risk. COX-2 inhibitors had a risk slightly above the non-selective NSAIDs, although this was not statistically significant. Aspirin use alone was not associated with increased risk.

The patients identified with acute urinary retention had higher comorbidities such as BPH, prostate cancer, neurologic disorders and prior UTIs. They also were using more anticholinergic drugs, narcotics, and benzodiazepines when compared to controls.

■ COMMENTARY

Prostaglandins are known to have an important role in urinary function, with synthesis in the bladder via the COX-2 pathway and involvement in the contractions that empty the bladder. One published case report of 3 patients suggested that starting treatment with COX-2 inhibitor drugs precipitated acute urinary retention.[1]

The Netherlands researchers searched their database for this association, and found not only that COX-2 inhibitors were associated with the new onset of acute urinary retention, but that the association with starting any NSAID treatment except aspirin had an even greater risk. Higher dosages carried more risk (although it was not a linear relationship), and acute urinary retention occurred most often with recent onset of NSAID therapy.

They did not find an association of acute urinary retention with daily aspirin therapy, another prostaglandin inhibitor, which they attributed to its use mainly in low doses for cardiac protection.

Although the risk found here is only an association and not definitively proved as a cause, and like all medical cases there were many other factors involved, this information nonetheless should make us all more alert to signs of urinary problems when we initiate NSAID therapy, particularly in high-risk patients. ■

Reference

1. Gruenenfelder J, et al. Acute urinary retention associated with the use of cyclooxygenase-2 inhibitors. *J Urol.* 2002;168:1106.

The Risk Predictive Value of the Coronary Artery Calcification Score in Middle-Aged Healthy Men

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: *In middle-aged, asymptomatic men, the presence of coronary artery calcification proved to have substantial, cost-effective, independent prognostic value that was incremental to measured coronary risk factors in its ability to predict incident coronary artery disease.*

Source: Taylor AJ, et al. Coronary Calcium Independently Predicts Incident Premature Coronary Heart Disease Over Measured Cardiovascular Risk Factors Mean Three-Year Outcomes in the Prospective Army Coronary Calcium (PACC) Project. *J Am Coll Cardiol*. 2005;46:807-814.

THE FRAMINGHAM RISK SCORE (FRS) IS AN EXCELLENT coronary artery heart disease (CHD) risk prediction tool.[1-4] In addition, recent guidelines have outlined the potential use of anatomically based CHD risk assessments, especially using electron-beam computed tomography (CT) to detect coronary artery calcium (CAC)[5,6] however, controversy still exists regarding whether, and to what extent, detection of CAC provides any incremental risk prediction beyond conventional CHD risk factor tools such as the FRS.

The Prospective Army Coronary Calcium (PACC) project was a prospective cohort study of US Army personnel which was designed to examine whether there was any incremental value of the CAC score above and beyond the FRC for the determination of CHD prognosis. CAC was found in 22.4% of men and 7.9% of women between the ages of 40 and 50 years (mean age, 43 years). Annual telephonic contacts over 1 to 6 years with the 2000 subjects were made and it was determined that 7 acute events occurred among the 364 men with CAC (CAC score of 10-44 in 2 subjects and > 45 in 5 subjects) and in only 2 of the 1263 men without CAC resulting in an 11.8-fold increase risk for incident CHD in subjects with CAC controlling for the FRS. These findings were highly significant suggesting that the presence of CAC in relatively young asymptomatic men provided substantial, cost-effective, independent prognostic value that was incremental to measured coronary risk factors in predicting incident CHD.

COMMENTARY

The independent predictive value of CAC had been in question since electron-beam computed tomography was introduced many years ago. The value of global coronary risk scoring algorithms such as the FRC in evaluating CHD risk has been fully accepted by most cardiologists however, there are some who feel that the FRC incompletely identifies CHD risk and may lead to systematic over estimation of risk especially in lower-risk populations.[7] A meta-analysis which examined the relationship between CAC, coronary risk factors and CHD events noted that many of the studies reported an independent relationship between CAC and either mortality or CHD events but that there was a substantial degree of variability in the reported strength of this relationship. The observed variability was thought to be due to the manner of risk factor assessment, the adjudication of outcomes and the inclusion of women in the cohort and therefore, the PACC project was designed to compare CAC scanning scores to measured risk factors in order to ascertain the true incremental value of CAC scanning in middle-aged men.

Generally expressed concerns about cost-effectiveness of CAC screening are certainly appropriate. The potential advantages of screening men age 40-50 included a generally lower prevalence of CAC in this age group thereby limiting the potential for over-detection of individuals identified as being at risk because of the dominant relationship between age and CAC score. The PACC study was underpowered to exclude relationships between CAC and CHD events in women; however, one study did suggest that such a relationship existed between CAC score and total mortality.[8] Obviously, further studies in larger female cohorts are needed but, for the time being, the incremental predictive value of CAC over conventional risk factors for premature CHD outcomes in middle-aged men appears to be meaningful although prospective, carefully controlled trials with larger numbers of both men and women are needed before CAC screening can be recommended for widespread use. Because of the obvious clinical benefit of detecting early CHF and because the cost effectiveness analysis suggested significant overall benefit, payers should consider paying for this screening tool, at least for asymptomatic men older than age 40, at this time.

Reference

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2. Greenland P, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. *Circulation*. 2000;101:E16-E22.
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Proton Pump Inhibitors Reduce the Bioavailability of Dietary Vitamin C

ABSTRACT & COMMENTARY

By Malcolm Robinson MD, FACP, FACG

Emeritus Clinical Professor of Medicine, University of Oklahoma College of Medicine, Oklahoma City

Dr. Robinson serves as a consultant for TAP, Pfizer, Janssen, Eisai, J&J-Merck, and Procter & Gamble, is on the speaker's bureau of Janssen, Eli Lilly, Solvay, TAP, and Aventis, and does research for Forest Labs, Wyeth-Ayerst, AstraZeneca, and Centocor.

Synopsis: *Even a short course of omeprazole reduces plasma vitamin C levels in healthy volunteers, and this effect would be expected to be magnified in* H. pylori*-positive individuals who have low pre-treatment vitamin C levels.*

Source: Henry EB, et al. Proton pump inhibitors reduce the bioavailability of dietary vitamin C. *Aliment Pharmacol Ther.* 2005;22:539-545.

Known to be an essential nutrient, vitamin C is actively secreted by healthy gastric mucosa and is present in the gastric lumen as ascorbic acid (its reduced form). With higher gastric pH values, far lower levels of ascorbic acid and vitamin C are present in the stomach (and vitamin C is known to be unstable at high pH values). Henry and colleagues have shown that patients with *H. pylori* infections treated with omeprazole for 2 months exhibit both lowered gastric juice and plasma vitamin C concentrations.[1] The present study was designed to evaluate healthy subjects both with and without *H. pylori* infections. Dietary intake of vitamin C was carefully estimated, and all subjects had HPLC assessments of total plasma ascorbic acid and vitamin C levels before and after 4 weeks of omeprazole 40 mg daily. *H. pylori*-positive subjects had lower baseline dietary vitamin C intake (35.9 mg vs 130.9 mg for the *H. pylori*-negative subjects), and *H. pylori*-positive subjects also had lower baseline plasma vitamin C concentrations (16.3 µg/mL vs 25.6 µg/mL). After 4 weeks of omeprazole, both groups exhibited further decreases in mean plasma vitamin C levels (approximately 12%). Gastric pH studies confirmed the expected augmented pH elevation in the *H. pylori*-positive group (pH > 4 for 50.7% of the interval in *H. pylori*-negative subjects vs 92.3% for the *H. pylori*-positive subjects.

COMMENTARY

Dr. McColl's group hypothesized that the lower vitamin C dietary intake in the *H. pylori*-positive subjects was due to their lower socioeconomic status. Although it is possible that lowering of vitamin C plasma levels in normal individuals without *H. pylori* might have untoward clinical consequences, the risks in *H. pylori*-positive individuals would be expected to be substantially higher. Low vitamin C status is a known risk factor for gastric cancer, and it is certainly possible that vitamin C deficiency might synergize with *H. pylori* to augment gastric cancer risk in infected individuals. PPIs are among the most widely used medications, and they are generally accepted as extremely safe. However, a few studies now exist that suggest that the pharmacological effects of PPIs on acid secretion may not ultimately prove to be quite as benign as some have thought. Careful chronic prospective surveillance of PPI recipients should continue. ■

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Pharmacology Update

Zolpidem Tartrate Extended Release Tablets (Ambien CR™)

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

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

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

THE FDA HAS APPROVED AN EXTENDED-RELEASE form of zolpidem. The drug delivery system consists of a coated 2-layer tablet, one releases the drug immediately and the other provides a slower release. Zolpidem extended-release (zolpidem ER) is marketed by Sanofi-Synthelabo as Ambien CR™.

Indications

Zolpidem ER is indicated for the treatment of insomnia characterized by difficulty falling asleep and/or difficulty staying asleep.[1]

Dosage

The recommended dose is 12.5 mg immediately before bedtime. As with the immediate-release formulation, zolpidem should not be taken with or immediately after a meal.[1,2] The tablet should be swallowed whole and not divided, chewed, or crushed. The 6.25 mg dose is recommended for the elderly, debilitated, or those with hepatic insufficiency.[1]

Zolpidem ER is available as 6.25 mg and 12.5 mg tablets.

Potential Advantages

The duration of effect may be longer with zolpidem ER compared to the immediate-release formulation.

Potential Disadvantages

The longer systemic exposure to the drug potentially could lead to greater daytime residual effects.

Comments

Zolpidem is a nonbenzodiazepine sedative hypnotic with selective binding for the 1 subunit of the GABA(A) receptor (ie, benzodiazepine 1 receptor) and generally does not alter sleep architecture.[3,4] It reduces sleep latency and increases total sleep time and is generally well tolerated.[4] The extended-release formulation is marketed at 25% higher dose (ie, 12.5 mg and 6.25 mg vs 10 mg and 5 mg). This combined with the extended-release formulation provides a higher systemic exposure to the drug and a delay of about an hour to reach the same plasma level compared with the immediate-release formulation. The 2 formulations have similar elimination half lives.[1] The efficacy of zolpidem extended-release was shown in two placebo-controlled, 3-week studies in adult patients with primary insomnia. One study used 12.5 mg in patients aged 18-64 (n = 212) and the other used 6.25 mg in elderly patients (> 65 yrs) (n = 205). In the assessment of next-day residual effects, next-day somnolence was reported in 15% of zolpidem ER patients compared to 2% for placebo. There were no published studies comparing the 2 formulations. The wholesale cost of zolpidem ER is $2.82 per tablet for both strengths.

Clinical Implications

As the patent of zolpidem approaches expiration, the manufacturer has introduced an extended-release formulation in an attempt to maintain market share of the most commonly prescribed sleeping aid. Zolpidem ER does not appear to offer any substantive clinical advantages over the immediate-release formulation that is expected to be available generically later in 2006. ■

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CME Questions

15. Vitamin C and PPI therapy and *H. pylori* have which of the following relationships:

a. PPI therapy decreases plasma vitamin C in both *H. pylori*-positive and negative recipients.
b. *H. pylori*-positive individuals seem to exhibit lower dietary vitamin C intake and decreased blood levels of vitamin C.
c. Omeprazole administration seems most likely to lead to vitamin C deficiency-related problems in *H. pylori*-positive individuals.
d. Vitamin C deficiency and *H. pylori* infection may be co-factors in the pathogenesis of gastric adenocarcinoma.
e. All of the above

16. Coronary artery calcium scoring measured by electron-beam CT scanning:

a. is of substantial prognostic value in middle-aged men.
b. is abnormal in 22.4% of men and 7.9% of women aged 30-40 years.
c. will probably prove to be an effective method for screening men and women.
d. at increased risk of developing symptomatic CHD.
e. All of the above.

17. Which of the following drug classes have been associated with the onset of acute urinary retention?

a. Anti-cholinergic drugs
b. COX-2 inhibitors
c. Nonsteroidal Anti-inflammatory drugs
d. All of the above
e. None of the above

18. Which of the following patients is most likely to be sleepy?

a. A young woman being treated for depression.
b. A woman with a body mass index of 21 kg/m^2
c. A snoring man of normal weight with no medical history and a normal physical examination.
d. A woman taking thyroid replacement therapy, with no other medical problems.
e. A healthy 66-year-old man

Answers: 15 (e); 16 (d); 17 (d); 18 (a)

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Clinical Briefs

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Are NSAIDs Different in the CHF Impact?

TRADITIONAL NSAIDS HAVE THE potential to cause fluid retention and BP elevations, either of which can worsen heart failure (CHF). Coxibs, such as celecoxib and rofecoxib, have recently come under close scrutiny due to increased cardiovascular risk associated with their use, though not specifically increased CHF risk. Whether there might be a difference in impact upon CHF outcomes for persons who receive celecoxib or rofecoxib vs non-selective NSAIDs has not been widely studied, although an earlier trial indicated that receipt of a coxib prescription at discharge for CHF incurred an increase risk of rehospitalization in the next year compared to not receiving such treatment.

Hudson et al used a hospital database of discharge summaries in Quebec, Canada which included 2,256 persons aged 66 or older with CHF who had been prescribed an NSAID, celecoxib, or rofecoxib. The primary end point of the study was the risk of death and recurrent CHF. Comparing NSAIDs, rofecoxib, and celecoxib, the risk of CHF for celecoxib and traditional NSAIDs was no different. However, the hazard ratio for the primary end point was 1.27 for persons receiving rofecoxib vs celecoxib. Similarly, the hazard ratio for mortality was 1.44 for rofecoxib vs celecoxib. These data suggest that celecoxib is safer in persons with CHF than rofecoxib. Newer coxibs are being developed, and differences amongst them may be highly relevant. ■

Hudson M, et al. BMJ. 2005;330:1370.

Treatment of HTN and Cognitive Function: SCOPE

THE STUDY ON COGNITION AND prognosis in the Elderly (SCOPE) trial was comprised of adults aged 70-89 years (n = 4,937) with mild-to-moderate hypertension (HTN). Patient inclusion criteria for this double-blind, randomized, placebo-controlled trial also entailed cognitive function testing with the Mini Mental State Examination (MMSE). Persons with mildly reduced cognitive function have been shown to have greater risk for development of frank dementia. Whether treatment of HTN in persons with mild cognitive impairment might reduce the development of further cognitive decline is not well established.

SCOPE study subjects were treated with candesartan (CAN) or placebo for HTN. In the placebo group as well as the CAN treatment group, subjects were allowed open-label treatment with antihypertensives to control BP to a level of < 160/90, initially with HCTZ 12.5 mg/d. Subjects were subgrouped by mental status scores into high cognitive function (MMSE Score ≥ 27/30) versus lower cognitive function (MMSE = 24-27/30).

After a mean of 3.7 years treatment, the incidence of frank dementia was higher in persons who had entered the trial with lower cognitive function at baseline. However, decline in cognitive function in this group was less amongst those treated with CAN than placebo (P = 0.04). As has been seen in other trials, CAN treatment reduced non-fatal stroke (28%).

These data are encouraging that in addition to reducing macrovascular end points, CAN treatment of HTN in persons with mildly impaired cognitive function may reduce further cognitive function decline. ■

Skoog I, et al. Am J Hypertens. 2005;18:1052-1059.

Impact of Job and Marital Strain on BP

A HIGH LEVEL OF JOB STRESS (JOB) HAS been linked both to increased frequency of hypertension (HTN) and worsened cardiovascular outcome. Marital stress has also been associated with impact upon both daytime and nighttime BP, as measured by 24-hr ambulatory BP (ABPM).

Study subjects (n = 248) were normotensive, predominantly white Canadian adult men and women (age, 40-65) without evidence of CAD, diabetes, or kidney disease at enrollment. Job diversity included clerical, technical, nurses, and physicians. Subjects were in established relationships and employed full time. Marital strain was measured by the Dyadic Adjustment Scale; job strain was measured using the Job Content Questionnaire. Both are validated stress scales. All subjects underwent ABPM on a 'typical' work day.

By multiple regression analysis, job strain and marital strain independently were both statistically significant variables for higher BP. The combination of job strain and marital strain were synergistic in their association with higher BP impact. Encouragingly, lower marital strain was associated with a mollifying effect upon JOB-induced BP elevation. ■

Tobe SW, et al. Am J Hypertens. 2005;18:1046-1051.

In Future Issues: **CABG vs. Stenting—Which is Better?**