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INSIDE

Tired of Diets? Sleep and Lose Weight!

ABSTRACT & COMMENTARY

Synopsis: *Young people who sleep less are more likely to be and to become obese.*

Source: Hasler G, et al. *Sleep*. 2004;27:661-666.

This was a prospective, interview-based study of people from the Zurich Cohort Study, a group of individuals selected to be at risk for psychiatric disorders.[1] All participants underwent screening with a sociodemographic questionnaire and the Symptom Checklist 90-R (SCL-90-R), which is a psychological symptoms questionnaire.[2] Initially, 292 men and 299 women were enrolled. They underwent the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology (SPIKE) interview,[1] measurement of Body Mass Index (BMI), and questions about sleep duration and quality at the ages of 27, 29, 34, and 40. Of the 591 who started the study, only 367 were followed until age 40. Short sleep was defined as less than 6 hours a night.[3] Data were analyzed in several ways, including by gender, for SCL-90-R high and low scorers, and by sociodemographic variables. Associations between sleep duration and obesity were analyzed both using BMI as a continuous variable and using BMI as a dichotomous (yes/no for obesity) variable.

On average, women slept more than men at all ages (eg, 7.7 hrs vs 7.13 hrs at age 27), and sleep duration declined with age (eg, 7.13 hours at age 27 and 6.9 hours at age 40 for men). Those of low socioeconomic status slept less than those of higher socioeconomic status. Scores on the SCL-90-R did not correlate with sleep duration. Thus, analyses were controlled for gender, age, and socioeconomic status, but not for SCL-90-R score.

At ages 27, 29, and 34, those who reported sleeping less than 6 hours were more likely to be obese at those ages, and at previous and future ages, up until the age of 40. For example, a person who slept less than 6 hours at the age of 29 had odd ratios for obesity of 8.1 (CI, 1.8-37.4), 4.6 (CI, 1.3-16.5), and 11.8 (1.6-86.5) at ages 29, 34, and 27, respectively. There was a linear inverse relationship between

VOLUME 26 • NUMBER 14 • JULY 29, 2004 • PAGES 105-112

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sleep duration and BMI. Impaired sleep quality, insomnia, awakenings during sleep, and daytime sleepiness were not associated with obesity. The relationship between sleep and obesity was not significant at the age of 40.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Obesity is quickly overtaking smoking as the most prevalent preventable cause of death in the United States. As more interest focuses on weight loss, we are queried daily about the relative utility of the Atkins diet, the South Beach diet, gastric reduction surgery, etc, etc. Our patients are desperately looking for weight loss plans that do not involve consuming fewer calories or burning more of them. Perhaps we should tell them about the relationship between sleep, weight, and appetite. This is a new story, and much is still unclear, but 2 important themes are emerging:

1. sleep has something to do with metabolism and appetite regulation;
2. our bodies have a U-shaped relationship with sleep, just as they do with calories: both too much and too little are bad for you.

Sleep duration has consistently been shown to have a U-shaped relationship with morbidity and mortality, with the lowest risk being seen for those sleeping 7 or 8 hours a night, and increasing risk for either ends of the U. For example, Ayas showed that women sleeping fewer than 6 or more than 9 hours of sleep a night were at increased risk of coronary events[4] and mortality,[5] essentially confirming earlier work by Kripke.[6]

In cross-sectional studies of sleep duration and metabolic problems, investigators have chosen to focus on the short sleep end of the U. And there is plenty of circumstantial evidence that short sleep is associated with obesity. Take the 2 sleep-deprived groups of college freshmen (with their freshman 15) and medical interns, for example. In fact, the increase in obesity in this country has paralleled a decrease in the average amount of nightly sleep obtained by Americans. Ayas previously showed an association between short sleep and diabetes,[3] and von Kries demonstrated that prevalence of obesity decreases by duration of sleep even in young children, controlling for other risk factors.[7]

Biologically, it's important to remember that circadian rhythm and metabolic function are closely related. Things that disturb sleep also disturb circadian rhythm, which in turn disturbs metabolic function. Sleep-deprived normal people have increased cortisol levels, worsened glucose tolerance, reduced leptin levels (appetite suppressant hormone) and increased caloric intake compared with when they are rested.[8,9]

The current study by Hasler and colleagues is important because it is prospective, includes a well-defined cohort, and strictly controls for most known confounders. It also shows a "dose response" relationship between BMI and sleep duration, although the dose-response curve is fairly flat between 5 and 9 hours of sleep. The relationship between sleep and weight weakened at the age of 40, which suggests that what we do in early life builds a foundation for further health. Although you may feel like saying "duh" at this point, maybe we should be advising our patients that getting enough sleep is important for current and future health, including affecting their risk of obesity in mid-life.

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

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Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $249
(Student/Resident rate: $125).

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The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours.
This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Brunton is a consultant for Andrx, Reliant, and AstraZeneca and serves on the speaker's bureau of Janssen, Schering, Aventis and AstraZeneca. Dr. Hall is a consultant for Aventis. Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3-M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim. Dr. Ost is on the speaker's bureau of Merck, Roche, and Boehringer Ingelheim and does research for the American Lung Association. Dr. Phillips serves on the speaker's bureau of Cephalon, Boehringer Ingelheim, Merck, Res Med, and GlaxoSmithKline and is a consultant for Boehringer Ingelheim, Wyeth-Ayerst, and Res Med. 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. Drs. Chan, Elliott, Grauer, Karpman, Wiese, and Wilke report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

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But before you tell your patients to go on the Rip van Winkle Diet, remember that, at least for cardiovascular disease and for all-cause mortality, too much sleep is as bad as too little.[4-6] Moderation in everything, including sleep. The magic number is 7 hours. ■

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Treat Erectile Dysfunction with Lifestyle Changes

ABSTRACT & COMMENTARY

Synopsis: *A randomized, controlled trial of obese men, ages 35 to 55, with erectile dysfunction showed that weight loss and increased physical activity allowed 31% to regain sexual function and most reduced their cardiac risk factors.*

Source: Esposito K, et al. *JAMA*. 2004;291:2978-2984.

In the Health Professionals Follow-up Study, moderate-to-severe erectile dysfunction was reported by 12% of men younger than 59 years, 22% of men aged 60-69 years, and 30% of men older than 69 years.[1] This study from Italy followed 110 obese men with erectile dysfunction (ED) over 2 years. They were relatively young (ages, 35-55) and did not have the comorbidities of diabetes and hypertension. Fifty five of the men were randomly assigned to an intervention group to achieve a weight loss of 10% or more through calorie control, behavioral counseling, and increased physical activity (walking, swimming, or aerobic games). They were seen monthly. Men in the control group were given general oral and written information about healthy food choices and exercise and were seen bimonthly. All men were obese with BMIs ranging from 30 to 49. About 30% of men in both groups smoked.

After 2 years, men in the intervention group had significant decreases in body weight, BMI, waist-to-hip ratio, blood pressure, levels of glucose, cholesterol and triglycerides, and a significant increase in HDL cholesterol. There was no significant change in any of these parameters in the control group. Erectile function improved in the intervention group but remained stable in the control group. 31% of the men (17) in the intervention group regained normal sexual function, while only 3 men regained normal function in the control group.

Saigal from UCLA provides an editorial in the same issue putting these findings into perspective.[2] These study patients were young and did not have the common comorbidities seen in common primary care practice. However, the findings suggest that significant ED may be prevented by early intervention in obesity and a sedentary lifestyle in younger men.

■ **COMMENT BY JOSEPH E. SCHERGER, MD, MPH**

Ever since sildenafil (Viagra™) was released in 1998, men have come in reporting some degree of erectile dysfunction in large numbers. Now, 3 related medications are dominating the commercial airwaves. If we neglect to get a history of erectile dysfunction during an office visit, patients often ask for samples as part of an "Oh by the way. . . ." We can only wonder how much of this is recreational use, based on insecurity, or a desire for better sex. While these medications may improve sexual function, they do not improve the patient's overall health. Weight loss and increased physical activity definitely will improve health, and it is rewarding to see that it also improves sexual function.

With the epidemic of obesity and metabolic syndrome going on in our communities, this study gives an added incentive for men to achieve better health. While it is easier, albeit more expensive, to take a pill, improved sexual function without medication can be added to counseling for weight loss and increased physical activity. Whether or not the patient ends up trying medication for ED, we should be aggressive in helping obese men reduce their cardiac risk factors and improve their quality of life. ■

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The Natural History of Prostate Cancer

ABSTRACT & COMMENTARY

Synopsis: *Among patients with early, localized prostate cancer, the mortality rate accelerated after 15 years.*

Source: Johansson JE, et al. *JAMA*. 2004;291:2713-2719.

These researchers from Sweden report their latest findings from their population-based cohort study of men with early, localized, prostate cancer. In previously published updates, they demonstrated that tumor grade at diagnosis is an excellent predictor of local and distant progression (1989);1 that the 10-year, disease-specific survival rate was 87% (1992);2 and that the corrected 15-year survival rate of 81% was similar in patients with deferred treatment and in those who received initial treatment (1997).3 The current update extends the follow-up to an average 21 years with only 9% of the original cohort still living.

The subjects were recruited from 1977 to 1984. The world in which this study was conceived, commenced, and conducted is different than the one in which we find ourselves today. There was no prostate-specific antigen (PSA) testing or mass screening for prostate cancer. Cancer was diagnosed by digital rectal exam (DRE) or serendipitously discovered after transurethral resection (TURP) for suspected benign prostatic hypertrophy. Standard of care was to treat tumors confined to the prostate with no distant metastases with watchful waiting. During the first 2 years of the study only patients with highly differentiated tumors were included in the no treatment group. After that, patients younger than 75 years old with moderately or poorly differentiated tumors were randomized to no treatment or local treatment. A total of 654 Swedish males with newly diagnosed prostate cancer began the study; 233 were in the untreated group. They were an average of 72 years old (range, 41-92). Almost half (48%) of the diagnoses were made at TURP. The tumors were predominantly highly differentiated (65%); only 9% were poorly differentiated. The tumors were either T0 or T1-2.

All patients were followed until death or September 1, 2001. At periodic follow-up visits, clinical examinations, blood work, and bone scans were performed. If their cancers become symptomatic, they were treated with exogenous estrogen or orchidectomy. Patients were offered fine-needle biopsy every 2 years during the first 6 years of follow-up. There were biopsy specimens from 178 (80%) of patients. Over the course of the study, 21 (of 178) patients had their tumors downgraded from high to moderate, 7 from moderate to low, and 3 from high to low differentiation.

After an average of 21 years of follow-up, 89 (40%) of subjects had tumor growth through the prostate capsule; 39 (17%) developed distant metastases; and, 35 (16%) had a cancer-related death. Patients who were = 70 years at diagnosis had a greater degree of death from cancer (22/101, 22%). There was no difference in mortality between patients who were identified at TURP and those by DRE; however, poor differentiation was highly predictive (56%). During the first 15 years of follow-up, the prostate mortality rate held steady at 15 per 1000 person-years; during this follow-up period, it shot to 44 per 1000. Degree of differentiation was associated with rate of mortality (10 per 1000 for highly differentiated tumors, 194 per 1000 for poorly differentiated). After multivariate analysis, tumor grade, but not age at diagnosis or tumor stage, was significantly associated with prostate cancer mortality. On the other hand, the rate of local progression did not increase over time.

COMMENT BY ALLAN J. WILKE, MD

This has been a time of surprises in prostate cancer research. The main surprise in this study was the increased rate of death after 15 years of follow-up. What explains this? Johansson offer several hypotheses, including tumor de-differentiation. Editorialists suggest that the introduction of new technology since to onset of the study has allowed for more complete recognition of prostate cancer recurrence. Other explanations are the development of a different clone of prostate cancer or cardiovascular disease secondary to estrogen therapy among those patients who developed symptomatic prostate cancer. A couple of weeks before this article was published in *JAMA*, the *New England Journal of Medicine* published[4] (and *Internal Medicine Alert* reviewed[5]) an article that looked at the incidence of prostate cancer among men with PSA = 4.0 ng/mL (15%), the level that is commonly assumed to be the upper end of normal (*see Clinical Briefs on page 112 of this issue*). We had high hopes when PSA testing was first introduced that it would identify those men who would benefit from prostate cancer treatment. Free PSA determination was supposed to improve this. I don't think we're there yet, but we may be getting closer. The current iteration is PSA velocity; men with PSA levels that double[6] or increase greater than 2.0 ng/mL/yr[7] have shorter times to death from prostate cancer.

Before applying these findings to your patients,

remember the study's limitations. All of the subjects were northern Europeans. None of the cancers were discovered though PSA testing. To make this information really useful, we need to know what the lead-time is between cancer detectable by PSA and by DRE or TURP. An important observation that the authors make incorporates the findings of another recent prostate study. In that study,[8] radical prostatectomy reduced death from prostate cancer by half. If that finding were applied to the 35 subjects in this study who died of prostate cancer, 18 patients would have benefited; the other 205 would not have. ■

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COX-2 Inhibitor Controversy

ABSTRACTS & COMMENTARY

Synopsis: *Current rofecoxib use was associated with a higher risk of acute myocardial infarction or admission for heart failure compared to celecoxib.*

Sources: Soloman DH, et al. *Circulation*. 2004;109: 2068-2073; Mamdani M, et al. *Lancet*. 2004;363: 1751-1756.

CYCLOOXYGENASE-2 INHIBITORS ARE ASSOCIATED with less gastrointestinal bleeding than nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), but concern about their cardiovascular effects have arisen. Thus, Solomon and colleagues conducted a case-controlled study of 54,475 patients older than 65 years old identified in a state-sponsored pharmaceutical benefits program for elderly or disabled low-income individuals from 1998-2000. Patients with diseases that may have obscured the relationship between COX-2 drugs and cardiovascular disease were excluded. The case defining event was hospitalization for acute myocardial infarction (AMI), determined by chart review, which was found in 10,895. For each AMI, 4 controls were found and matched for age and sex. Logistic regression analyses were used to assess the relative risk of AMI in patients taking rofecoxib, celecoxib or no NSAIDs. The relative risk of AMI in those on rofecoxib compared to celecoxib was 1.24 (95% CI, 1.05-1.46; $P < .02$) and compared to no NSAID was 1.14 (1.0-1.3; $P = .054$). The effect was related to drug dose: rofecoxib 25 mg or less vs celecoxib 200 mg or less (OR, 1.21; 1.01-1.44; $P = .036$) or rofecoxib > 25 mg vs cel coxib > 200 mg (OR, 1.7; 1.07-2.71; $P = .026$). Also, risk of AMI with rofecoxib was related to duration of therapy: 1-30 days (OR, 1.4; 1.12-1.75; $P = .005$) and > 90 days (OR, .96; 0.72-1.25; $P = 0.8$) compared to celecoxib for a similar duration. Celecoxib was not associated with a higher risk of AMI vs no NSAIDs. Soloman and colleagues concluded that current rofecoxib use was associated with a higher risk of acute myocardial infarction compared to celecoxib or no NSAID use. The risk was treatest during the first 90 days of use, but not thereafter and was higher with doses > 25 mg/d.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Although a boon to those with arthritic conditions, concern about adverse cardiac effects based upon the VIGOR study has been a source of continued controversy. In the VIGOR study, rofecoxib 50 mg was compared to naproxen 1000 mg in patients with rheumatoid arthritis. The risk of AMI was elevated in the rofecoxib-treated patients, but aspirin use was prohibited. Other studies have either confirmed or denied this finding, but all had significant limitations. Studies of celecoxib have been generally neutral on AMI risk with a few exceptions. This large observational study certainly puts the onus back on rofecoxib (Merck) to prove that AMI risk is not increased vs celecoxib (Pfizer). Mechanistically, it is not clear why one drug would be more of a problem than the other. Both inhibit COX-2, which decreases the beneficial vasodilatory and platelet effects of prostacyclin, leaving intact the platelet aggregation and vasoconstriction effects of COX-1. Perhaps rofecoxib is just more potent since other studies have shown increased blood pressure on rofecoxib vs celecoxib. The dose relationship would support this as well. Also, the increased risk associated with initial therapy probably has to do with ferreting out the susceptible patients, suggesting that avoiding these drugs in high-risk cardiac patients would make sense.

There are limitations to this study. First, Medicare databases are not always accurate, especially with disease classification. Second, this is a retrospective observational study that could be biased by unrecognized confounders. Third, some patients may have taken their coxib PRN. Finally, the generalizability of a low-income elderly or disabled population may be suspect. However, until a defini-

tive randomized controlled study is completed, it would be advisable to avoid coxibs and especially high doses of rofecoxib in high risk ischemic heart disease patients.

The second study by Mamdani and colleagues is also a retrospective observational study of subjects older than 65 years old in Ontario, Canada, who were divided into 3 cohorts: users of rofecoxib, celecoxib, or non-selective NSAIDs. The case defining event was hospital admission for congestive heart failure. Using a community control group of non-NSAID users proportional hazzard models were constructed accounting for comorbidity. Compared to the controls, rofecoxib and non-selective NSAID users had a higher rate of admissions for heart failure (RR, 1.8; 1.5-2.2; and 1.4; 1.0-1.9, respectively) but not celecoxib (1.0, 0.8-1.3). Among patients with no heart failure admissions for 3 years, only rofecoxib increased the risk of subsequent admission relative to the controls (1.8, 1.4-2.3). Of note, COX-2 users were more likely to have pre-existing cardiovascular disease based upon their history of other drug use. Also, patients without previous use of cardiovascular medications were more likely to be put on them in all the NSAID groups. Soloman et al concluded that there is a higher risk of admission for heart failure among users of rofecxib and non-selective NSAIDs, but not with celecoxib.

COMMENT BY MICHAEL H. CRAWFORD, MD

The Mamdani study is interesting because this same group using the same database were unable to demonstrate a difference in AMI rates between refecoxib and celecoxib, but in that study patients with NSAID use < 30 days were excluded. This is likely the most vulnerable timeframe based upon the Solman study above. In this study, they avoided that mistake and found that the risk of heart failure admission was higher on refecoxib and non-selective NSAIDs vs celecoxib (number needed to harm 14, 14, 24, respectively). Also, patients with no history of cardiovascular medication use were more likely to end up on them in the NSAID users. These are important findings given that 28% of Ontario seniors were prescribed these medications.

We have known for many years that non-selective NSAIDs may exacerbate heart failure by causing salt and water retention, but this study suggests that heart failure may even by precipitated for the first time with these drugs, especially rofecoxib. They suggest that rofecoxib may be more risky because of its long half-life and tendency to accumulate in the body, but believe caution is advised with all NSAIDs in patients at risk for heart failure. Also, their data are consistent with other studies showing that rofecoxib increases blood pressure more than other NSAIDs. This may contribute to heart failure initiation or decompensation.

This retrospective observational study suffers from the problem of bias due to unrecognized confounders. Also, this study had recognized confounders in that the coxib users were likely to have a higher incidence of pre-existing cardiovascular disease. In addition, no dosage data were available, but interestingly, < 10% of subject on rofecoxib were on < 25 mg/day. In summary, it would appear that the use of coxib drugs should be used with caution in patients at high risk for ischemic heart disease events or heart failure. Rofecoxib doses > 25 mg/day in particular should be avoided in such patients. ■

Dr. Crawford is Professor of Medicine, Associate Chief of Cardiology for Clinical Programs, University of California, San Francisco.

Pharmacology Update

Trospium Chloride Tablets (Sanctura™)

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

A NEW QUATERNARY AMMONIUM COMPOUND HAS been approved for the treatment of overactive bladder. Trospium is a nonselective antimuscarinic agent that reduces the tonus of smooth muscle in the bladder. It has been available in Europe for more than 20 years and is manufactured by Maduas AG in Germany and marketed in the United States as Sanctura™ by Odyssey Pharmaceuticals Inc and Indevus Pharmaceuticals Inc.

Indications

Trospium is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.[1]

Dosage

The recommended dose is 20 mg twice daily. It should be taken on an empty stomach or at least 1 hour before meals. Dosage modification is recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in geriatric patients 75 years or older. A 20 mg dose once daily is recommended for these patients.[1]

Trospium is available as 20 mg tablets.

Potential Advantages

Trospium does not appear to cross the blood brain barrier and does not affect CYP450 metabolism.[1,2] In

contrast, oxybutynin and tolterodine have potential drug-drug interactions with CYP3A4 and CYP2D6 respectively. About 60% of the absorbed drug is excre ed unchanged in the urine and therefore a large percent is available to the bladder.[1]

Potential Disadvantages

Most common side effects associated with trospium are dry mouth (20.1% vs 5.6% for placebo) and constipation (9.6% vs 4.6%). Asymptomatic, non-specific T-wave inversions were observed more often than with placebo or moxifloxacin during electrophysiology studies. The clinical significance of this effect is not known.[1]

Comments

The approval of trospium is based on 2 US, placebo-controlled, 12-week studies in patients with overactive bladders (n = 523,648) and one 9-month open label extension.[1] In the placebo-controlled studies, trospium showed a statistically significant decrease in mean urinary frequency and urge incontinence episodes.[1,3] In addition, mean urinary void volume, voiding urge severity, and urination during day and night were improved compared to placebo. Improvements were also detected with the travel, social relationships, and emotional health subscales of the Incontinence Impact Questionnaire.[3] In a long-term comparative tolerability and efficacy study (52 weeks) trospium (20 mg twice daily) was reported to be comparable in efficacy in terms of urodynamic variables to oxybutynin (5 mg twice daily) but better tolerated in terms of dry mouth symptoms.[4] Similarly trospium (20 mg twice daily) was reported to be comparable to but better tolerated than oxybutynin (5 mg 3 times a day) in patients with spinal cord injury and detrusor hyper-reflexia.[5] Trospium (20 mg twice daily) reported a greater decrease in frequency of mictuation per 24 hours compared to tolterodine (2 mg twice daily) with similar frequency of moderate-to-severe dry mouth (7% vs 9%).[6] The price of trospium was not available at the time of this review.

Clinical Implications

Overactive bladder is characterized by urgency, urge urinary incontinence, frequency, or nocturia. About one-third of patients with overactive bladder have urge incontinence and two thirds do not. Urge incontinence is much more common in women.[7] Antimuscarinics have been considered the mainstay of treatment for overactive bladder. Two recent reviews, however, suggest that the magnitude of clinical effect is small and of questionable clinical value.[8,9] Antimuscarinic drugs generally seem to have similar efficacy but may differ in frequency of side effects. Since muscarinic receptor M3 subtypes that mediate cholinergic contraction of the detrusor muscles are found in the bladder and salivary gland, dry mouth is a common side effects associated with these drug. Different drug delivery systems have been developed to reduce this side effect, and in general, extended release formulations have a lower frequency compared to immediate release formulations.[10,11] Extended release tolterodine (4 mg) appear to have a lower frequency of dry mouth than extended release oxybutynin (10 mg).[12] Based mainly on indirect comparison, the frequencies appear similar between trospium and tolterodine extended release. Transdermal oxybutynin may have the lowest frequency of dry mouth but has a discontinuation rate of about 10% due mainly to application site reaction (eg, pruritus and erythema).[13] It is not known how antimuscarinic drugs in general would compare to bladder retraining or how combination therapy would compare.[8] ■

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CME Question

3. In the prospective Zurich Cohort study, individuals who slept less were more likely to be:

a. men, of lower socioeconomic status, older, and obese.
b. women, of higher socioeconomic status, younger, and obese.
c. women, of lower socioeconomic status, older, and nonobese.
d. men, of lower socioeconomic status, younger, and nonobese.
e. women, of higher socioeconomic status, younger, and nonobese.

Answer: 3(a)

By Louis Kuritzky, MD

Prevalence of Prostate Cancer Among Men with a Prostate-Specific Antigen Level < 4.0 ng/mL

The prostate cancer prevention trial enrolled 18, 882 men to evaluate whether an alpha-reductase inhibitor, finasteride, could prevent incident prostate cancer in men with normal PSA levels(< 3.0 ng/mL). Half of the men in this trial received placebo, but nonetheless subsequently underwent prostate biopsy at the end of the 7-year study. A PSA level of < 4.0 in asymptomatic men is commonly observed as the boundary for consideration of prostate cancer, although it has been recently suggested that the threshold be reduced to 2.5 ng/mL.

The end-of-study prostate biopsy identified prostate cancer in 15.2% of the 2950 men in the placebo group. Eighty percent of tumors identified had low Gleason scores (6 or less). There was a significant difference in PSA levels between the men who were determined to have prostate cancer and those with normal biopsies (PSA mean, 1.78 vs 1.34). Additionally, rate of rise of PSA was associated with risk of prostate cancer.

At first glance, such data might stimulate clinicians to consider lowering the threshold for prostate biopsy. However, since the currently available trial data have not provided convincing evidence that intervention based upon PSA-screening has had a favorable effect upon all-cause mortality, whether more vigorous attention to lesser PSA levels will ultimately benefit men remains unknown. ■

Thompson IM, et al N Engl J Med 2004;350:2239-2246.

Mirtazapine for Reducing Nocturnal Itch in Patients with Chronic Pruritus

Pruritus is a commonplace complaint of persons with dermatological disorders like psoriasis, atopic dermatitis, and chronic urticaria. Nocturnal itch interrupts sleep and compromises quality of life. Traditional antihistamines offer some relief, but may be limited by daytime somnolence. The concept that antidepressants might be beneficial for pruritus is bolstered by the observation that doxepin, a tricyclic antidepressant, has been found to be a dramatically more potent histamine receptor blocker than even the most potent traditional antihistamines (eg, cetirizine, loratadine). Mirtazapine, an antidepressant, has been reported to effectively treat pruritus of cholestasis, lymphoma, and uremia.

Three patients with intractable pruritus (failed treatment with high dose antihistamines, and some other agents) responded promptly to mirtazapine 15 mg/d, including one patient who had not responded to doxepin. Mirtazapine has potent H1-antihistamine activity, but it is theorized that its adrenergic antagonism may also be involved in pruritus relief. This small pilot trial provides hope that larger trials will confirm the efficacy of mirtazapine for this and other pruritus disorders. ■

Hundley JI, Yosipovitch G. J Am Acad Dermatol 2004;50:889-891

A Factorial Trial of Six Interventions for the Prevention of Postoperative Nausea and Vomiting

As many as 1 out of 3 post-surgical patients suffer nausea and vomiting (N&V), unless prophylaxed with antiemetic pharmacotherapy. Worldwide, 75 million persons per year undergo a surgical procedure requiring anesthesia, hence optimizing N&V outcomes is a epidemiologically compelling. Not only are the symptoms troublesome, but N&V leads to serious postsurgical consequences such as aspiration, wound dehiscence, and esophageal rupture.

Six different treatments, alone and in combination, were evaluated in 5199 patients: ondansetron, dexamethasone, droperidol, substituting propofol for other anesthetics, nitrous oxide omission from the multi-drug anesthetic regimen, , and remifentanil substitution for fentanyl.

The antiemetics (ondansetron, dexamethasone, droperidol) reduced N&V by about 26%, propofol by 19%, and nitrous oxide omission by 12%. Fentanyl substitution by remifentanil was not effective to reduce N&V. Combined interventions were additive to reduce N&V. Since all interventions except fentanyl substitution were beneficial, it is recommended that initial choice be based upon safety and cost. Patients at low-risk might uncommonly require prophylaxis, whereas high-risk patients could benefit from a combination of treatments. ■

Apfel CC, et al N Engl J Med 2004;350: 2441-2451.

In Future Issues: What do we Really Know about Adiponectin?