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The Long-Term Effects of Intimate Partner Violence

ABSTRACT & COMMENTARY

Synopsis: *Abused women are more likely to suffer adverse physical health consequences.*

Source: Campbell J, et al. *Arch Intern Med.* 2002;162:1157-1163.

To investigate health problems among women who had experienced intimate partner violence (IPV), this group from Johns Hopkins mailed invitations to participate in a survey of women's health to 21,426 women who were members of a Washington, DC health maintenance organization. The 2535 women who responded were phoned to describe the survey and were informed that they would be questioned about abuse. After appropriate exclusion, 2005 women were enrolled.

The study was conducted from January 1, 1995, through December 31, 1997, but the abuse could have occurred as far back as 1989. The study group was administered a modified version of the Abuse Assessment Screen. Defining IPV as "physical and/or sexual assault by a husband, partner, ex-husband, or ex-partner," Campbell and colleagues identified 201 women who answered affirmatively to 1 or more of 3 questions: "Have you ever as an adult been physically abused by a husband, boyfriend, or female partner? Have you ever been hit, slapped, kicked, pushed or shoved, or otherwise physically hurt by a current or previous husband, boyfriend, or female partner? Have you ever been forced into sexual activities by a husband, boyfriend, or female partner?" From the group of women who answered no to the questions and who were in an intimate relationship, 240 were randomly selected. These 2 groups were then interviewed in depth. They were administered the general health perceptions subscale of the Medical Outcomes Study 36-Item Short-Form Health Survey and the Miller Abuse Physical Symptom and Injury Scale, and were queried about specific gynecologic, chronic stress-related, and central nervous system problems.

The 2 groups were similar in age, but otherwise significantly different. The abused women were more likely African-American, divorced or separated, less well educated, and have household incomes less than $50,000. (These demographic variables are likely not independent. That is, women are more likely to leave an abusive relationship

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than one where they are happy and subsequently have reduced household income. Similarly, lower education is reasonably related to lower household income.) The abused women were more likely to rate their health as poor and less likely to rate it excellent. They had more headaches, back pain, sexually transmitted diseases, vaginal bleeding, vaginal infections, pelvic pain, painful intercourse, urinary tract infections, loss of appetite, abdominal pain, and digestive problems.

The group of abused women was subdivided into those who had been sexually abused and those who were not. Women who were sexually abused reported more chronic stress-related and central nervous system problems than women who were abused, but not sexually, and women who were not abused.

COMMENT BY ALLAN J. WILKE, MD

This study is not without its weaknesses. There was no information provided about the nearly 19,000 women who chose not to answer the invitation. This is a potential flaw that could indicate bias (ie, the women who responded may be different from the women who didn't). The women's health problems and abuse were self-reported. There was no information on abuse occurring in childhood, which presumably could have had an effect on current health status. Despite this, this article adds to the growing literature of IPV. The Family Violence Prevention Fund (endabuse.org) estimates that annually there are 960,000 incidents of domestic violence to 3 million women. This compares to the 107,300 new cases of colon cancer the American Cancer Society estimates occur annually. Whether it is called IPV, domestic violence, or battering or spousal abuse, it has reached epidemic proportions. As conscientious primary care physicians, we screen for many illnesses and conditions, including colon cancer. It is high time that we screen for IPV. Campbell et al recommend that we ask 3 previously validated questions:[1]

1. Thinking back over the past year, on any occasion were you hit, slapped, kicked, raped, or otherwise physically hurt by someone you know or knew intimately, such as a spouse, partner, ex-spouse or partner, boyfriend, girlfriend, or date?
2. Considering your current partners or friends, or any past partners or friends, is there anyone who is making you feel unsafe now?
3. In the past year, have the police ever been called to your home because of a fight or argument, no matter who was fighting or who was at fault? ■

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1. Koziol-McLain J, et al. *Am J Prev Med.* 2001;21(2): 93-100.

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 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.

Back issues: $20. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

THOMSON

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Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $289
(Student/Resident rate: $145).

Multiple Copies
1-9 additional copies: $215 each; 10 or more copies: $191each.

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Internal Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of January 1, 2002. This volume has been approved for up to 40 prescribed credit hours. Credit may be claimed for one year from the date of this issue.
The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours.

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Is the Juice Worth the Squeeze?

ABSTRACT & COMMENTARY

Synopsis: *Results of a cost-effectiveness study comparing 5 monotherapy treatments for rheumatoid arthritis: methotrexate, leflunomide, etanercept, sulfasalazine, and no therapy.*

Source: Choi HK, et al. *J Rheumatol.* 2002;29:1156-1165.

THIS STUDY EVALUATED THE COST EFFECTIVENESS OF 5 monotherapy options for treating rheumatoid arthritis (RA) in methotrexate-naïve patients. Previously

published data were used to create a decision analysis comparing cost and effectiveness for each treatment regimen. For each treatment option, 5 factors were used to determine which option was the most cost effective: 1) probability of treatment success; 2) direct cost of therapy (administering and monitoring therapy); 3) indirect costs of therapy (lost productivity due to disease morbidity); 4) probability of side effects; and 5) expected cost of side effects. For each treatment option, Choi and colleagues used past studies to estimate the cost of achieving a 20%, 50%, or 70% treatment response (as defined by the American College of Rheumatology [ACR] response criteria).

The most cost-effective drug was methotrexate, costing $10,926 in total costs per 6 months. Choi et al also performed a sensitivity analysis: varying each variable to determine if the outcome of the most cost-effective drug would change. With even minor changes in the variables used in the analysis, sulfasalazine was indistinguishable from methotrexate in cost effectiveness.

Leflunomide cost more than methotrexate and sulfasalazine and was not more effective.

Etanercept was the most efficacious therapy, but also the most expensive, costing $16,165 per 6 months.

In order for the additional efficacy of etanercept to be considered cost effective, an incremental improvement of a 20% ACR remission of $40,000 would have to be acceptable.

COMMENT BY JEFF WIESE, MD

The recommended treatment for RA is a disease-modifying agent in addition to symptomatic relief (nonsteroidals, steroids). Once-a-week methotrexate has been the treatment standard, but newer agents have been introduced.[1] Many of these agents have shown increased efficacy when compared to methotrexate.[2-4] This study addresses an important question: Is the expense of these newer agents (both in cost and side effects) worth the additional efficacy?

This study used an extensive sensitivity analysis to determine what is the most cost-efficacious choice for the treatment of RA. While etanercept is more efficacious, it is not more cost-effective than methotrexate unless paying $40,000 per additional ACR 20% response is considered acceptable. Based on the sensitivity analysis, it was impossible to determine whether sulfasalazine or methotrexate was more cost effective.

This study also compares the cost effectiveness of methotrexate vs. no therapy. Because of the significant surgical and medical morbidity of RA, and the expected loss of productivity, using no therapy was less cost effective than early treatment with methotrexate.

The studies used to generate the data for these analyses only included methotrexate-naïve patients. Patients that have been previously exposed to methotrexate without a successful response are less likely to show a response the second time; this would reduce the cost-effectiveness of methotrexate. ■

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Secondary Prevention with Flu Vaccine

ABSTRACT & COMMENTARY

Synopsis: *Influenza vaccination at the time of hospital admission for coronary events or procedures may reduce the rate of subsequent events and death.*

Source: Gurfinkel EP, et al. *Circulation.* 2002;105:2143-2147.

Epidemiologic studies have shown an increase in myocardial infarction (MI) and cardiovascular death during influenza outbreaks. Thus, Gurfinkel and the FLUVACS study group conducted a randomized, prospective, multicentered, parallel-group controlled, single-blind study of flu vaccine in 200 patients with acute MI within 72 hours and 101 patients for elective percutaneous coronary intervention (PCI) during the winter of 2001 in the Southern Hemisphere. Patients enrolled in the treatment group received a unique flu vaccine against 3 flu strains intramuscularly. Follow-up telephone visits were done at 1 and 6 months. The incidence of cardiovascular death was 2% in the vaccine group and 8% in the controls ($P = .01$). The triple end point of mortality, MI or rehospitalization for recurrent angina requiring angioplasty or bypass surgery was also lower in the vaccine group—11% vs 23% ($P = .009$). There was no essential difference in these results when the 2 groups of patients were considered separately. Gurfinkel et al concluded that influenza vaccination at the time of acute MI or elective PCI may reduce the risk of recurrent ischemic events and death for 6 months during the flu season.

COMMENT BY MICHAEL H. CRAWFORD, MD

This interesting report is described by Gurfinkel et al as a pilot trial, but since it was clearly positive, it was the leading clinical report in a recent issue of *Circulation*. Basic research supports that prevention of viral infections may be beneficial in patients with coronary atherosclerosis. In animal models, viral infections can cause or accelerate atherosclerosis development and this effect can be blocked by vaccination. Also, viral titers have been correlated with restenosis rates after PCI in humans. There are several molecular mechanisms that may explain the atherogenic effects of viral infections including augmented inflammation, alterations in cholesterol metabolism, enhanced oxidation, and changes in the coagulation system. At this time we do not fully understand the molecular basis of these observations.

Although this is a pilot trial, it is hard to argue against recommending a flu shot for everyone with acute MI or undergoing PCI and perhaps everyone with coronary artery disease. They are approved, recommended for the elderly, relatively inexpensive, and fairly safe. So we can add flu shots to the long and growing list of therapeutic agents recommended for secondary prevention. We are truly in the polypharmacy era in cardiovascular care. ■

Dr. Crawford is Professor of Medicine, Mayo Medical School, Mayo Clinic, Scottsdale, Ariz.

Eye Strain Headache?

ABSTRACT & COMMENTARY

Synopsis: *In the current study, there appeared to be no difference in headache characteristics nor was there a difference in the relative frequencies of migraine, tension-type, or other primary headache disorders.*

Source: Gil-Gouveia R, et al. *Headache.* 2002;42:256-262.

PATIENTS COMPLAINING OF HEADACHE OFTEN CLAIM 1 of 3 things: sinus disease; brain tumor, or simply that their eyeglasses no longer work. The International Headache Society (IHS) does recognize headaches associated with refractive errors (HARE) but notes that their importance is widely overestimated. The diagnostic criteria for HARE are as follows:

a. uncorrected refractive errors;
b. mild headaches in the frontal region and within the eyes; and
c. pain absent on awakening and aggravated by prolonged visual tasks at the distance or angle where vision is impaired.

The current observational-interview study was undertaken to compare the overall headache frequency in healthy patients with refractive errors (n = 105) compared to normal controls (n = 71). The overall headache frequency between groups was similar (45% vs 52%). There appeared to be no difference in headache characteristics nor was there a difference in the relative frequencies of migraine, tension-type, or other primary headache disorders. Of note, there was a trend suggesting that improvement in headache in the patients with refractive error was associated with correction of vision. Only 7 patients fulfilled IHS criteria for HARE and 3 of these improved with correction of vision.

COMMENT BY JEFFREY REICH, MD

While there are methodological flaws in this small study, it is reassuring to find that, contrary to popular belief, headaches are only rarely identified in individuals with refractive errors. In patients with chronic headache, proper correction of vision should be considered as one of several factors. ■

Dr. Reich is Assistant Professor of Neurology, New York Presbyterian Hospital-Cornell Campus, New York, NY.

The Risk of Hospitalization and Near-Fatal and Fatal Asthma in Relation to the Perception of Dyspnea

ABSTRACT & COMMENTARY

Synopsis: *Asthmatic patients with low POD had a 10-fold increased risk of emergency department visits, hospitalizations, near-fatal asthma attacks, and deaths when compared to patients in the normal POD group.*

Source: Magadle R, et al. *Chest.* 2002;121:329-333.

TO PREVENT DEATHS FROM ASTHMA, IT IS IMPORTANT to identify patients who may be at risk of a fatal attack. Large variations in perception of respiratory symptoms may be observed from one asthmatic patient to another.[1] Reduced perception of dyspnea (POD) may result in a delay in instituting appropriate therapy and, thus, constitute a risk factor for severe exacerbations of asthma. By measuring POD, it may be possible to iden-

tify this subset of patients who are at risk for near fatal and fatal attacks allowing more aggressive management in these patients.

Patients (n = 113) attending an outpatient clinic had their POD measured using the Borg scale while breathing against a resistive load. Patients were followed up at 3-month intervals for a total of 8 visits and all hospitalizations, near fatal, and fatal attacks were recorded. Near fatal attacks were defined as attacks of asthma requiring treatment with mechanical ventilation or resulting in unconsciousness and severe respiratory failure. The reference standard was established by measuring POD in 100 age-and-sex matched controls. Normal POD was defined as the mean ± 1 standard deviation. Patients maintained a record of their prebronchodilator morning peak expiratory flow rates, β2 agonist use, and use of their other regular asthma medications including inhaled corticosteroids, theophylline, and oral corticosteroids for the first 4 weeks.

There were 67 (59%) patients with a normal POD, 17 patients (15%) with a high POD, and 29 patients (26%) with a low POD. Patients with low POD tended to be older (42 ± 5.4 years vs 39 ± 4.8 years, and 32 ± 4.9 years in the normal and high POD groups), and were more likely to be female (62% vs 45% vs 59%). The duration of asthma was longer in the low POD group when compared to patients in the normal POD and high POD group (21 ± 5 years vs 15 ± 4.6 years vs 12 ± 4.1 years, respectively). Severe asthma was present in 8 of 29 (27.5%) patients in the low POD group compared to 10 of 67 (14.9%) patients in the normal POD group and 4 of 17 (23.5%) in the high POD group. Patients in the low POD group had more emergency department visits than the normal and high POD groups (32 vs 8 vs 14 respectively; $P < 0.01$), were hospitalized more frequently (22 vs 4 vs 3; $P < 0.001$), had more incidents of near-fatal asthma (13 vs 2 vs 1; $P < 0.001$), and more deaths (6 vs 1 vs 0; $P < 0.001$).

COMMENT BY DAVID OST, MD, & NAJMA USMANI, MD

Despite advances in our understanding and treatment of asthma, mortality from asthma continues to rise, unlike mortality from other common treatable conditions.[2] To prevent death from asthma, it is important to identify the subset of patients who are most at risk for a fatal attack. It has been shown that such patients may have a decreased hypoxic response accompanied by a blunted POD.[3] As shown in this study, low POD is associated with adverse events. Though Magadle and colleagues recommend measuring POD at least once in asthmatic patients, the test is not available in routine practice and is done mostly in a research setting. Unfortunately, a history of near fatal attack that requires hospitalization and mechanical ventilation is the strongest single predictor of subsequent death from asthma.[4] Though POD cannot be measured routinely in this subset of patients, it may be that some of these patients have low POD contributing to their poor outcomes. Aggressive objective measures of disease activity such as daily peak flow recording, education on warning symptoms, and patient management plans may be of use in this setting. ■

Dr. Usmani is a Fellow in Pulmonary and Critical Care Medicine, North Shore University Hospital and Nassau University Medical Center, Manhasset, NY.

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Statins May be Good for Everybody!

ABSTRACT & COMMENTARY

Synopsis: *The analysis of 2 secondary prevention trials with pravastatin demonstrate that pravastatin lowered cardiac mortality and morbidity in diabetics who had LDL cholesterol levels below 125 mg%.*

Source: Sacks FA, et al. *Circulation.* 2002;105:1424-1428.

In 2 large secondary prevention studies of pravastatin, risk reduction was not significant in participants who had low baseline LDL-C concentration (ie, < 125 mg/dL).[1] Sacks and colleagues conducted an exploratory analysis of participant characteristics, lipid risk factors, and risk reduction in subgroups of these studies.

There were 13,173 participants with coronary heart disease (CHD); 2607 had baseline LDL-C < 125 mg/dL. Those with LDL-C < 125 mg/dL were more likely to be diabetic (15% vs 9%), hypertensive, male, have higher triglycerides, lower HDL-C and similar body mass index (BMI). During a 5.8 year (mean) follow-up, HDL-C and triglycerides were both significantly stronger predictors of recurrent CHD events in participants with LDL-C < than 125 mg/dL than in participants with LDL-C > 125 mg/dL.

The changes in LDL-C and HDL-C were more favorably effected in the nondiabetic group than in the diabet-

ic patients. Despite these findings, in diabetic subjects with low LDL-C, pravastatin decreased CHD events from 34% to 22% (relative risk, 0.56; $P = 0.004$), significantly different from the nondiabetic participants who did not benefit from pravastatin treatment.

Among patients with CHD who have low LDL-C, diabetics have a much higher rate of subsequent CHD event rates than do nondiabetics. Pravastatin reduced the event rate in diabetics to that of nondiabetic participants. The results also suggest enhanced therapeutic potential for improving HDL-C and triglycerides in patients with CHD who have low LDL-C concentrations.

COMMENT BY RALPH R. HALL, MD, FACP

The clinical benefits of statins have been primarily attributed to their lipid lowering effect. But as Young and Tsao note in a recent editorial, "subgroup analysis of large clinical trials indicates that statin treated individuals have significantly less cardiovascular disease than patients with comparable serum cholesterol levels" who are not receiving statins.[2]

Statins are known to have many functions other than their lipid lowering effects. They have beneficial effects on inflammation, cellular migration, proliferation, and survival. In the Scandinavian Simvastatin Survival Study, simvastatin reduced the risk of bone fracture. So as Young and Tsao point out, "it is clear that statins have significant noncholesterol lowering effects, both in the vascular and nonvascular systems." Statins improve endothelial function in nondiabetics but recent studies indicate that this may not be the case in diabetes.[3]

It is important to note the short comings of this study. Sacks et al cautioned that the risk reduction in patients with diabetes was not a prespecified hypothesis, but rather one that emerged from exploratory analysis of patient subgroups. Consequently, despite strong probability values in risk reduction, the observation supporting the use of pravastatin in diabetic patients with LDL-C levels < 125 mg% may have been due to chance.

The number of patients that physicians have to treat in order to prevent an event is very important in the diabetic patient. The cost of drugs to treat glucose levels, lipids, hypertension, and congestive heart failure is overwhelming for these patients. It is not clear, at this time, that all diabetics with low LDL-C should be treated with statins. Until further studies confirm these benefits, the guidelines established by the National Cholesterol Education Program still apply.[4] ■

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Pharmacology Update

Xyrem—A New Drug for Cataplexy

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

THE FDA HAS APPROVED SODIUM OXYBATE FOR THE treatment of patients with cataplexy associated with narcolepsy. Originally marketed as a dietary supplement, sodium oxybate is also known as gamma hydroxybutyrate or GHB. The drug is notorious as a street drug, popular among young adults due to its ability to cause relaxation and euphoria,[1] and has been dubbed the "date rape drug" by the press. Still, sodium oxybate has been anxiously awaited by the 20,000-50,000 narcoleptic patients who suffer from cataplexy. To assure appropriate prescribing, sodium oxybate will be distributed directly to the patient from one central pharmacy. It will be marketed under the name of Xyrem by Orphan Medical Inc.

Indications

Sodium oxybate is indicated for the treatment of cataplexy in patients with narcolepsy. It is contraindicated in patients currently being treated with sedative-hypnotics.[2]

Dosage

The recommended dose is 2.25 g at bedtime and again 2.5-4 hours later. The dose may be increased to 9 g/d in increments of 1.5 g/d after 2 weeks. The first dose should be taken while in bed and the second dose while sitting in bed. Each dose of sodium oxybate is diluted with 2 ounces (60 mL) of water. It should be taken on an empty stomach as food significantly reduces bioavailability. The effective dose is 6-9 g/d with 9 g being most effective. Doses greater than 9 g/d should not be taken.[2] Patients should not engage in any activity requiring alertness for at least 6 hours after taking this drug. Concomitant use of alcohol and other sedatives should be avoided.

Sodium oxybate is supplied as 500 mg/mL in a 180 mL bottle including a measuring syringe and dosing cups. Diluted preparations should be taken within 24 hours.

Potential Advantages

Sodium oxybate has been shown to reduce the fre-

quency of cataplexy attacks. Patients with a mean of 23.5 cataplexy attacks per week at baseline had a median reduction of 16 attacks per week with the 9 g/d dose and a reduction of 10 attacks per week with the 6 g/d dose.[2,3] In patients with a low frequency of cataplexy, (4/week) attacks were eliminated.[2] The frequency of inadvertent naps/sleep attacks and nighttime awakening were significantly improved with the 9 g dose.[3]

Potential Disadvantages

Sodium oxybate has significant abuse potential. It has been used as a recreational drug for about a decade. It produces relaxation and euphoria and has become popular as "liquid ectasy" and as a "date rape" drug.[1] Common side effects (vs placebo) include dizziness (32% vs 6%), nausea (15-34% vs 6%), and incontinence (6-14% vs 0%). The drug has also been associated with depression, confusion, and other neuropsychiatric events.[2] Abuse can lead to serious CNS side effects (eg, seizures, respiratory depression) that have resulted in coma and death as well as drug dependence and withdrawal symptoms.[2]

Comments

The efficacy of sodium oxybate was studied in 2 randomized, double-blind, placebo-controlled, 4-week studies involving a total of 185 patients. Eighty to 85% of these were being treated with CNS stimulants. Sodium oxybate (mainly the 9 g dose) was shown to significantly reduce cataplexy episodes. In more severe cases (mean of 23.5 attacks/week), the frequency was reduced by about two thirds. Attacks were eliminated in less severe cases (4 attacks/week). In addition, daytime sleepiness, inadvertent daytime naps/sleep attacks, and nighttime awakenings were also improved.[2,3] The mechanism of action is unclear but some postulate that it may serve as a neurotransmitter/neuromodulator and improve the restorative nature of nocturnal sleep. Sodium oxybate is and has been used as a recreational drug and carries with it a significant risk for abuse. The drug is available only through restricted distribution from a central pharmacy and will not be available in retail pharmacies. As condition for approval, the FDA required numerous risk management components. These include restricted distribution, a medication guide, documentation and verification of prescriber and patient education, maintenance of patient and prescriber registries, specific prescription handling and shipment directions, and a post marketing evaluation program. Prescribers and patients may call a toll free number for information on sodium oxybate (1-877-67-XYREM). Sodium oxybate solution is a Schedule III, federally controlled substance.

Clinical Implications

Narcolepsy is a lifelong disorder affecting about 120,000 people or about 1-2/2000 in the United States.[4] It is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, and sleep disturbance with serious personal, social, and economic implications. Cataplexy, which affects up to about 40% of these individuals, is a sudden loss of skeletal muscle tone (often dropping of the jaw) without loss of consciousness. These are often triggered by bursts of laughter, elation, embarrassment, anger, or sexual arousal. Defects in the orexin (hypocretin) A and B system have been hypothesized as the cause of this disorder.[5] Narcolepsy is generally managed with CNS stimulants (eg, amphetamines, methylphenidate, modafinil). While these are effective in improving daytime sleepiness, they do not affect cataplexy. Antidepressants, primarily tricyclic antidepressants, are the current standard treatment for cataplexy. There are, however, currently no published comparative studies between sodium oxybate and antidepressants. Sodium oxybate does offer an effective alternative. ■

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CME Questions

11. Abused women are more likely to report all of the following symptoms, *except*:

a. chest pain.
b. headache.
c. pelvic pain.
d. abdominal pain.
e. back pain.

12. Which of the following is true for a 40-year-old man presenting with rheumatoid arthritis?

a. Etanercept is the most efficacious therapy and, therefore, is the most cost-effective therapy.
b. Because of the high cost of side effects and drug monitoring, providing no therapy is more cost effective than methotrexate.
c. Methotrexate and sulfasalazine are equally cost effective in treating rheumatoid arthritis.
d. Methotrexate is the most cost-effective therapy in both patients who have not taken methotrexate, and those that have.

By Louis Kuritzky, MD

Orlistat in Overweight Patients with Type 2 Diabetes

Recently, it has been acknowledged that metformin (MET), in contrast to insulin secretagogues or insulin supplementation, is weight neutral or even associated with weight loss. Unfortunately, most DM2 patients are, or will be, on more than one medication, which may complicate weight management.

Of the 2 medications currently available for long-term management of obesity, both sibutramine and orlistat (ORL) have been shown to provide statistically significant weight reduction in DM2. Whether such effects might extend to persons specifically receiving DM2 treatment with metformin has not been previously studied. In particular, since both MET and ORL are associated with GI symptoms, the tolerability as well as efficacy of this combination merits clarification.

In this study, ORL (n = 249) or placebo (n = 254) was administered t.i.d to patients on stable doses of MET. Some patients were also receiving sulfonylureas (SFU) in addition to MET. Insulin, thiazolidinedione, or alpha-glucosidase treatments were exclusionary from the study. Patients were treated for 1 year.

ORL was associated with clinically important, as well as statistically significant improvements in A1c (mean = 0.9 decrease); LDL, triglycerides, and blood pressure were all favorably affected in comparison to placebo. Mean weight loss was 4.7 kg on ORL (vs 1.8 kg, placebo). Although GI complaints were more frequent in the ORL group, withdrawal due to adverse events was actually more frequent in the placebo group. In overweight diabetics on MET, ORL is well tolerated and effective for multiple factors pertinent to diabetic control. ■

Miles JM, et al. Diabetes Care. 2002; 25:1123-1128.

Sleep Attacks in Patients Taking Dopamine Agonists

The term "sleep attack" is defined as ". . . an event of overwhelming sleepiness that occurs without warning or with a prodrome sufficiently short or overpowering to prevent protective measures." It has already been recognized that dopaminergic drugs, such as those commonly used in Parkinsonism (eg, levodopa, ropinirole, bromocriptine), are associated with somnolence and motor vehicle accidents (MVA). Identification of the frequency of sleep attacks is relevant to risk reduction.

Homann and colleagues identified 20 publications that included suspect events (n = 124), further dividing them into definite, probable, and possible sleep attacks. Ten of 17 events occurring during driving lead to MVA; however, numerous attacks happened even during ambulatory activities, such as walking or standing.

In this review, as many as 30% of patients receiving dopamine agonists for Parkinson's disease (PD) had sleep attacks, regarded by Homann et al as a class phenomenon, rather than due to a specific agent. Additionally, dose reduction was not reliably associated with remission of sleep attacks, and of course could risk lesser symptom control of PD. It has been recommended that persons taking pramipexole and ropinirole not drive. Short of not driving, it is uncertain which measures should be exercised for Parkinson's patients taking other dopaminergic medications. Indeed, there remains some controversy about the existence of sleep attacks distinct from simple somnolence. The descriptions in this communication argue for the definition of sleep attacks as a separate entity. ■

Homann CN, et al. BMJ. 2002;324: 1483-1487.

Probiotics in Prevention of AAD

The consequences of antibiotic-associated diarrhea (AAD) are potentially far ranging. Though thoughtful antibiotic selection and application can reduce the frequency of AAD, numerous clinical situations will require antibiotics for which the likelihood of AAD is known to be significant. Probiotics (PRO) are microorganisms with therapeutic potential—some nonpathogenic organisms appear to inhibit the growth of pathogens. *Saccharomyces boulardii*, a nonpathogenic yeast, has been reported to destroy the receptor site for *C difficile* toxin A and B through a protease enzyme.

In this report, 9 double-blind, placebo-controlled trials were analyzed. Agents used included *S boulardii*, lactobacilli, and enterococcus. In each of the trials, the PRO was administered concomitantly with the antibiotics. Antibiotics studied included amoxicillin, clindamycin, and multi-drug regimens.

Concomitant PRO administration was associated with an approximately 60% reduction in odds ratio for AAD. PRO are well tolerated, without known serious adverse effects, and though they transiently colonize the gut, upon cessation of therapy they are generally rapidly cleared from the GI microbial population. This meta-analysis indicates PRO may offer valuable reductions in the frequency of AAD, and further study is suggested. ■

D'Souza AL, et al. BMJ. 2002;324: 1361-1364.

In Future Issues: Good News, Bad News—Sleep Apnea and Cardiovascular Risk