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INSIDE

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Who Knew? You Can Be Too Thin! Of Course, Most People Aren't…

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant for Cephalon, and serves on the speaker's bureaus for Resmed and Respironics.

Synopsis: *In a large study of American adults, all-cause mortality was lowest for those with a body mass index (BMI) of 20.0-24.9 kg/m^2.*

Source: Berrington de Gonzalez AB, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010;363:2211-2219.

This report results from a pooled analysis of 1.46 million white adults who were enrolled in 19 different prospective studies funded by the National Cancer Institute. To be included in this analysis, a study had to have started in 1970 or later, and had to include data about height, weight, and smoking status. Most studies also included information about pre-existing health conditions, alcohol consumption, cardiac disease, education, marital status, and physical activity. The investigators formatted these variables to be consistently classified across studies into standard categories. The cause of death was determined from death certificates or medical records. Analyses used proportional-hazards models, with age as the underlying time variable, and adjusted for alcohol intake, educational level, marital status, and physical activity. These investigators defined a BMI of 22.5-24.9 kg/m^2 as the referent category because of previous studies demonstrating this BMI was usually associated with the lowest mortality.

In the large, combined (1.46 million people) cohort, 58% were women, median age was 58 years, and median BMI was 26.2 kg/m^2. Smoking was inversely correlated with BMI; only 13% of the cohort were active smokers, though only 53% reported that they had

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never smoked. Pre-existing cancer and emphysema were more common in thinner people, but physical inactivity and lack of a college degree were both associated with a higher BMI.

The rate of death from any cause was lowest among those with a BMI of 22.5-24.9 kg/m^2, and the risk of death increased with both higher and lower levels of BMI. When the investigators excluded smokers and those with heart disease or cancer at baseline, the risk of death increased for a BMI > 25 kg/m^2, but decreased for a BMI < 22.5 kg/m^2. The hazard ratios by BMI for death for healthy women who never smoked are presented in Table 1 *(right)*; results were similar for men.

Further adjustment for alcohol consumption, physical activity, educational level, and marital status only slightly reduced the hazard-ratio estimates associated with a BMI ≥ 25 kg/m^2. The risk of a higher BMI was greater for younger people. The cause of death for a BMI ≥ 25 kg/m^2 was highest for heart disease and lowest for cancer.

The risk of death for those with lower (< 20 kg/m^2) BMIs declined as the length of follow-up increased, and was only significant for the very thinnest people (BMI < 18.4 kg/m^2) at 15 or more years of follow-up.

Table 1. Hazard ratios by BMI for death in healthy women who never smoked.

BMI (kg/m^2)	Risk Hazard Ratio for Death
25-29.9	1.13
30-34.9	1.44
35-39.9	1.88
40-49.9	2.51

■ COMMENTARY

This is not the first paper to show a relationship between obesity and death, of course, but it is the largest. Further, the authors were able to adjust for smoking and prevalent illness, which has not always been possible in many prior studies of the relationship between BMI and mortality.[1-4] The current study also confirms that being "merely" overweight (defined as a BMI between 25 kg/m^2 and 30 kg/m^2) is associated with an increased risk of death.[1,4,5] The authors note that although the data suggest that very thin people have increased risk of death in the short run, this risk is weak in the long run, and the association between low BMI and death was much weaker in physically active people. They interpret this to mean that the association between low BMI and death probably results from pre-existing disease.

The relevance of these findings is amplified by the fact that they apply to so many people. Two-thirds of United States adults are overweight or obese.[6,7] Among non-Hispanic persons in the United States, an estimated 11% of men and 17% of women had a BMI ≥ 35 in 2008.[7]

Sadly, there were more than five times as many deaths among participants in the highest BMI categories (BMI of 35.0-39.9 kg/m^2 and 40.0-49.9 kg/m^2) than in previous related studies,[1-5] because severe obesity has become more common.

Let's face it: Obesity and overweight are huge medical problems in this country. American ingenuity has responded in predictable ways. Weight Watchers is a $1.4 billion industry, with a vast array of options for the would-be thin person, including books, internet programs, special food products, and branded items on menus of some popular restaurant chains.[8] Just in time for the holidays, the highly successful Weight Watchers program just announced a new point system. And Weight Watchers works.[9] Of course, most insurance plans won't pay for Weight Watchers. They will, however, often pay for bariatric gastric reduction procedures — one of which has just been recommended by an FDA panel[10] to be approved for use in those who have a BMI of just 30 kg/m^2 — along with a medical complication. Is there something wrong with this picture?

For those of us on the front lines, the message is clear: Painful and time-consuming as it is, we must deliver the message that being overweight or obese kills. Since most of my patients have sleep apnea (and diabetes and hypertension), I have a great deal of experience with this endeavor. And most of it is pretty negative. Patients expect the doctor to tell them to quit smoking. But they

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Questions & Comments
Please call **Paula Cousins**, Senior Managing Editor, at (404) 262-5488.

Table 2. Items that contain about 250 calories.

2 1/2 apples
5 strips of bacon
20 oz of beer (1 3/4 cans)
10 carrots
1/6 quart ice cream
1/2 cheeseburger
10 oranges
5 chocolate chip cookies
20 oz of cola beverage (1 3/4 cans)
3 glasses of skim milk
2 1/2 fried eggs
1 fried chicken breast

Table 3. Activities that consume about 250 calories for a 150-lb person (more for a heavier person).

Walking 45 minutes
Bike riding 30 minutes
Swimming 22 minutes
Running 13 minutes
Sitting on the couch watching TV 3 1/4 hours
Climbing 12 flights of stairs

often don't expect to hear that they need to lose weight. In my experience, patients can and will punish the bearer of this news in a variety of ways, including (but not limited to) describing (in excruciating and time-consuming detail) what they eat, explaining (in excruciating and time-consuming detail) why they can't exercise, crying, or complaining to the hospital administrator. It helps to have a handout and a plan. Our handout includes a BMI chart so the patient can "do the math," rather than take my word for it. It also includes calorie charts for food and exercise *(see Tables 2 and 3, above)*, so that patients can get the message that it is easier not to take in calories than it is to expend them. But it's an uphill battle. I would be a much more popular doctor if I were better at this part of my job, or if I simply didn't take this part of my job so seriously.

It is likely that obesity now kills more Americans than cigarettes do. And, on that point, some parallels might be drawn. Just as we didn't make much progress against cigarette smoking until we stigmatized it, limited it, and taxed it, I doubt we will make much headway against obesity as long as we continue to pretend that it is a harmless lifestyle choice instead of a deadly, chronic, largely self-inflicted disease. ■

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The New Face of Hepatitis A

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: *Hepatitis A has been greatly reduced in the United States due to widespread vaccination, and most new cases are now the result of international travel.*

Source: The evolving epidemiology of hepatitis A in the United States. *Arch Intern Med* 2010;170:1811-1818.

Hepatitis A continues to be a significant illness, with an estimated 1.4 million new cases worldwide. In developing countries, children develop immunity after infection, so outbreaks are infrequent. In other countries, where children do not become immune from natural exposure, adult populations are susceptible and outbreaks can occur, including many countries in the European Union.

The U.S. Centers for Disease Control and Prevention (CDC) recruited states covering 30 million persons to participate in the Emerging Infections Program (EIP), which involved molecular testing of hepatitis A virus strains to more thoroughly describe the infections that do occur in the United States. For the years 2005-2007, 1156 cases of hepatitis A were reported, and 49% were from New York City. Of these, 39% were Hispanic. Most cases occurred in urban areas. The most common source of infection was international travel or being exposed to a traveler, with Mexico being the most common associated source. For patients reporting travel as their only known risk factor, 86 of 108 cases were traveling to their county of native birth. One outbreak in Minnesota was associated with a foodborne outbreak, but most others involved international travel as the most likely source. This was confirmed with molecular analysis, which showed that the strains from the travel-related cases were very similar to strains in the countries where the travel occurred.

Before vaccination was available for hepatitis A, only 4% of U.S. cases were associated with international travel; now 46% of cases are travel-related. The national vaccination strategy was expanded to all children age 2 years and older in 1999; by 2003, this resulted in a 76% decline in the incidence of hepatitis A overall, and an 87% decline in incidence among children age 2-18 years. Since 2006, national recommendations for hepatitis A vaccine include all children age 12 months or older in the United States.

■ COMMENTARY

This is a remarkable success story for the reduction of hepatitis A in the United States, from approximately 26,000 or more annual cases before the vaccine to only 600 cases during this study period. The disease in adults can cause major morbidity and even fatal liver failure. An interesting consequence of this success is that the disease now has a different epidemiology, changing from outbreak-associated to mainly sporadic cases associated with international travel.

It's important for clinicians to understand this change in the incidence of hepatitis A, because it means that preventive strategies must target international travelers as well as universal childhood immunization. The most high-risk group is persons returning to their native countries to visit family and friends.[1] Tourists and business travelers had a lower risk of infection. Ongoing surveillance of hepatitis A continues to be important so that we can understand where and when it occurs, and respond appropriately. ■

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Treating Sexual Dysfunction Related to Use of Antidepressants

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

This article originally appeared in the December 2010 issue of OB/GYN Clinical Alerts. At that time it was peer reviewed by Catherine LeClair, MD, Associate Professor, Department of OB/GYN, Oregon Health & Science University, Portland. Dr. LeClair reports no financial relationship to this field of study.

Synopsis: *In a prospective, randomized, double-blind, placebo-controlled trial of women taking SRI's, sildenafil treatment resulted in a reduction of sexual side effects.*

Source: Nurnberg HG et al. Sildenafil treatment of women with antidepressant-associated sexual dysfunction. *JAMA* 2008;300:395-404.

A study group of 98 patients was enrolled through seven centers to evaluate the efficacy of sildenafil in the treatment of sexual dysfunction associated with the use of selective and nonselective serotonin reuptake inhibitors (SRIs). The patients had to be previously sexually functioning, premenopausal, and successfully treated for their depression with an SRI, but with sexual dysfunction at the time of enrollment. Several validated scales of sexual functioning were used to assess outcomes with the primary outcome being changes on the Clinical Global Impression sexual function scale (CGI). In the 8-week parallel group study, patients took either placebo or sildenafil (50-100 mg flexible dosing schedule) prior to activity. The CGI score of women treated with sildenafil was 1.9 (95% confidence interval [CI], 1.6-2.3), while those

taking placebo scored on average 1.1 (95% CI, 0.8-1.5). Hormone levels were comparable and the rate of depression remission was also the same.

■ COMMENTARY

How often has a patient asked you, "Why isn't there a Viagra for women?" Well, there is … sort of. There was a minor blip on the radar screen of the medical news when this first came out in 2008, but the enthusiasm has somewhat died. The antidepressant-associated sexual dysfunction that we all encounter in our daily practices remains a challenge looking for an effective solution. As an editorial aside, I am particularly sensitive to this because of my skewed patient population that is heavy on chronic pelvic pain, antidepressant use, and sexual dysfunction. Particularly disconcerting is the repeated scenario in which patients prematurely discontinue their antidepressant therapy because of the sexual side effects. What are we to do?

We know that the phenomenon is common, i.e., the literature tells us that anywhere from 30% to 70% of patients on selective and nonselective serotonin reuptake inhibitors develop symptoms such as decrease in libido, vaginial lubrication, and sensitivity. In addition, women are also troubled by orgasmic dysfunction, dyspareunia, reduced sexual activity, and reduced satisfaction.

The relevance of the problem and the data in this article should be placed in proper perspective within the landscape of sexual dysfunction, which currently consists of four categories: sexual desire disorders (including hypoactive desire and aversion), sexual arousal disorders, sexual orgasmic disorders, and sexual pain disorders (dyspareunia and vaginismus). Whereas sildenafil is FDA-approved for arousal disorders in men, SRI-induced dysfunction is typically of the desire or orgasm type. To complicate the picture further, desire dysfunction (loss of libido) is the most common type of sexual dysfunction in females. If sildenafil works in women as it does in men, it should not directly affect libido, but should improve blood flow to the pelvic region. In men, this results in erection whereas in women, it would lead to more vasocongestion and vaginal lubrication, thereby simulating the normal physiologic response of arousal and reducing dyspareunia.

Even though the literature is not totally consistent in identifying a benefit for the use of sildenafil, it should be noted that this group of patients does show potential efficacy. Since we all see patients that might benefit from its use, knowing that there might be something available at least gives us another option to consider. As with men, the medication is used prior to sexual activity. This study started with 50 mg and allowed the patient to take up to 100 mg. In other studies involving male subjects, doses of up to 200 mg have been reported. When I offer this choice to patients, I typically start with the lowest dose, 25 mg, then increase from there.

Patient education is critical when considering applying these data. First, the clinician should recognize that depression itself can have a deleterious effect on sexual functioning. Also, an antidepressant, be it SRI or not, has the potential for adversely affecting libido and other aspects of sexual functioning. Sometimes, it becomes the proverbial "Which came first, the chicken or the egg?" quandary, trying to sort out what whether the sexual dysfunction antedated the use of the antidepressant or, more specifically, the SRI. The patient should be told specifically that the goal is not to increase libido directly. In men, it does not increase libido, but does increase blood flow to the penis, thereby generating the erection that allows the man to be sexually functional.

Other small series or case reports have suggested other approaches to these complaints, none of which has shown more than limited efficacy. The concept of a "drug holiday" in which the patient takes the SRI only on weekdays in order to be more sexually functional on the weekends has now been marginalized because of the tendency of the patient to be less compliant with taking the medication on a regular basis. Adding a non-SRI medication such as buproprion has shown limited success. Reports on yohimbine, urecholine, and periactin have been published. Any of you out there who has tried to deal with this problem has certainly found it frustrating and difficult.

Perhaps this report might allow some of us to step out and try it more often. We will continue to be asked by patients, so we might as well be open to new possibilities. As products are tested and new reports come out, we'll be watching. The testosterone patch has still not gotten here despite much anticipation. We know that women's

sexual functioning is a different issue when compared to men. As I tell my patients, "Men use sex as stress relief, while women need to have stress relieved before they can have sex." Yes, it's different, not as simple, but certainly worth our continued efforts. ■

Pharmacology Update

Dextromethorphan Hydrobromide and Quinidine Sulfate Tablets (Nuedexta™)

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

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

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

THE FDA HAS APPROVED THE FIRST TREATMENT FOR PSEUDOBULBAR affect (PBA). This condition is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying and is secondary to certain underlying neurologic diseases or injuries. This new combination product contains a N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 agonist, dextromethorphan, and a CYP 450 2D6 inhibitor, quinidine. The product will be marketed by Avanir Pharmaceuticals, Inc., as Nuedexta™ in the first quarter of 2011.

Indications

Dextromethorphan (DEX)/quinidine (QUIN) is indicated for the treatment of pseudobulbar affect.[1]

Dosage

The recommended dose is 1 capsule daily for 7 days and then 1 capsule every 12 hours.[1]

The product is available as capsules, each containing DEX 20 mg and QUIN 10 mg.

Potential Advantages

DEX/QUIN reduced laughing and crying episodes compared to placebo in patients with amyotrophic lateral sclerosis and multiple sclerosis.[1]

Potential Disadvantages

DEX/QUIN may cause dose-dependent QTc prolongation. It is contraindicated in patients with prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, heart failure, or risk of complete atrioventricular block (implanted pacemaker the exception).[1] Concomitant use of drugs that prolonged QT interval and are metabolized by CYP 2D6 is contraindicated. Common adverse events, compared to placebo, include diarrhea (13% vs 6%), dizziness (10% vs 5%), cough (5% vs 2%), vomiting (5% vs 1%), asthenia (5% vs 2%), peripheral edema (5% vs 1%), urinary tract infection (4% vs1%), influenza (4% vs 1%), increased gamma-glutamyltransferase (3% vs 0%), and flatulence (3% vs 1%). Thrombocytopenia and lupus-like syndrome have been associated with quinidine.

Comments

Dextromethorphan is a low-affinity, noncompetitive NMDA-receptor antagonist and sigma-1 receptor agonist. Quinidine, a potent CYP P450 2D6 inhibitor, blocks first-pass metabolism resulting in improved systemic exposure of dextromethorphan. The exact mechanism of action in treating pseudobulbar affect is not known. The efficacy was evaluated in a 12-week, randomized, double-blind, placebo-controlled study in patients with amyotrophic lateral sclerosis or multiple sclerosis.[1,2] The study randomized patients to DEX/QUIN 30 mg/10 mg (n = 110), DEX/QUIN 20 mg/10 mg (n = 107), or placebo (n = 109). The primary endpoint was patient's change from baseline in the number of PBA episodes of laughing and/or crying per day as recorded in the patient's diary. A secondary endpoint was the patient's change from baseline on Center for Neurologic Studies Lability Scale (CNS-LS). This is a 7-item self-assessment of PBA severity. With no clear clinical advantage with the higher dose, only the 20 mg/10 mg was approved by the FDA. DEX/QUIN 20 mg/10 mg showed a 49% reduction compared to placebo ($P < 0.001$). The 12-week mean change in daily episodes was -3.9 compared to -3.0 for placebo ($P = 0.0099$). There was a significant reduction from baseline CNS-LS compared to placebo (8.2 vs 5.7; $P = 0.011$). Remission was reported in approximately 50% of patients treated with DEX/QUIN compared to approximately 30% for placebo.[2] Remission was defined as absence of episodes throughout the final two weeks of the 12-week study. Dizziness and diarrhea were more common with DEX/QUIN compared to placebo (10.3% vs 5.5% and 13.1% vs 6.4%, respectively).[2]

Clinical Implications

Psuedobulbar affect is a disorder of emotional expression characterized by uncontrollable outbursts of laughing

and/or crying.[3] This disorder appears to occur in the setting of neurological diseases such as amyotrophic lateral sclerosis and multiple sclerosis. Current therapies include tricyclic antidepressants and selective serotonin reuptake inhibitors and may be considered in patients with depression.[3] DEX/QUIN is the first FDA-approved treatment for this condition. Whether the efficacy of this combination of drugs can be generalized to other causes of pseudobulbar affect not related to ALS or MS is not known. ■

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Brief Report

'Weekend Effect' and Stroke

By Matthew E. Fink, MD

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

This article originally appeared in the November issue of Neurology Alert. At that time it was peer reviewed by M. Flint Beal, MD, Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Beal reports no financial relationship to this field of study.

Source: Hoh BL, et al. Effect of weekend compared with weekday stroke admission on thrombolytic use, in-hospital mortality, discharge disposition, hospital charges, and length of stay in the Nationwide Inpatient Sample Database, 2002 to 2007. *Stroke* 2010; 41:2323-2338.

A stroke "weekend effect" on mortality has been noted in studies reported from countries other than the United States. The authors reviewed the U.S. National Inpatient Sample database from 2002 to 2007 for all emergency room admissions with ICD-9 classifications of acute ischemic stroke, to compare weekend vs. weekday stroke admission incidence of thrombolytic use, inhospital mortality, discharge disposition, hospital charges, and length of stay. Adjustments were made to correct for differences in age, gender, season, median income, payer source, comorbidities, hospital location, teaching status, and hospital size.

There were 599,087 emergency room admissions for ischemic stroke: 439,181 weekday admissions and 159,906 weekend admissions. Compared to weekday admissions, patients with acute ischemic stroke admitted on weekends were slightly more likely to receive thrombolytics (OR = 1.114; $P = 0.003$), incur higher total hospital charges (effect ratio = 1.001; $P < 0.001$), and have slightly longer lengths of stay (effect ratio = 1.021; $P < 0.001$). There was no difference in hospital mortality or disposition at time of discharge. ■

CME Questions

65. Obesity:
a. kills.
b. is defined as a BMI > 35 kg/m^2.
c. is decreasing in prevalence in the United States.
d. is safer for younger people than older people.

66. Which of the following groups in the United States is at highest risk for new cases of hepatitis A?
a. Restaurant workers
b. Business travelers to developing countries
c. Tourists traveling internationally
d. Travelers returning internationally to native countries
e. Children traveling internationally

67. Which of the following types of sexual dysfunction is most common in women?
a. Sexual arousal disorders
b. Sexual desire disorders
c. Sexual orgasmic disorders
d. Sexual pain disorders

Answers: 65. a, 66. d, 67. b.

CME Objectives

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

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

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
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Coenzyme Q10 for Peyronie's disease

Source: Safarinejad MR. Safety and efficacy of coenzyme Q10 supplementation in early chronic Peyronie's disease. *Int J Impot Res* 2010;22:298-309.

Peyronie's disease is an uncommon penile fibrotic disorder that most commonly affects young and middle-aged men. It is characterized by pain, deformity, or decreased capacity for intromission as a result of penile angulation. In contrast to chordee, the congenital abnormality in which ventral penile tissue defects prevent full expansion of the underside of the penis, resulting in a downward curvature upon erection, Peyronie's disease is an acquired fibrosis of the penis, which results in thickened penile plaques that prevent full erection. In whatever area of the penis such fibrotic plaques occur, that area will be unable to achieve full dilation and erection, resulting in angulation of the penis. There is no uniformly effective treatment for Peyronie's disease, although surgical correction is often effective.

Fibrotic plaque analysis in Peyronie's disease has demonstrated early oxidative inflammation, followed by creation of fibrotic scar. Since coenzyme Q10 has been shown to have antioxidant capacity, a clinical trial of its efficacy in early Peyronie's was intuitively appealing.

Men with early Peyronie's disease (n = 186) were randomized to coenzyme Q10 300 mg/day or placebo for 24 weeks. At trial end, there was a statistically significant reduction in plaque size, penile curvature, and improvement in sexual function in the active treatment group. Because coenzyme Q10 is a very well tolerated intervention with no known serious adverse effects (there were no reported drug-related adverse events or discontinuations), it offers a promising alternative for persons with Peyronie's disease. ■

Impact of using A1c to diagnose pre-diabetes

Source: Mann DM, et al. Impact of A1c screening criterion on the diagnosis of pre-diabetes among U.S. adults. *Diabetes Care* 2010;33:2190-2195.

The dramatic increase in type 2 diabetes (DM2) seen in the last decade is predictably going to become even more evident: Although 24 million Americans currently have DM2, more than twice as many have pre-diabetes (p-DM2). Historically, persons with p-DM2 who are untreated progress to frank DM2 at a rate of 7%-10% per year.

Until 2010, p-DM2 was diagnosed based upon the presence of either impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. Since 2010, the ADA has indicated that an A1c of 5.7%-6.4% qualifies as p-DM2. This tool has been welcomed by the primary care community because it does not require fasting, and can be obtained during any routine office visit. The limitation of A1c, however, is that it does not necessarily capture all the persons who would have been identified had either a fasting blood glucose or postprandial glucose (or both) been obtained; data from NHANES indicate that a substantial number of persons with IFG will not have an abnormal A1c, and vice versa. For instance, of 51.7 million NHANES subjects with IFG, only 23 million have an A1c that meets p-DM2 criteria.

All of the diagnostic markers for p-DM2 are used in an effort to identify the pathophysiologic derangements at a point in time where intervention might change disease progression. IFG, IGT, and A1c identify overlapping, but not identical, populations. Because clinicians will commonly have access to fasting glucose levels obtained concomitantly with other labs (e.g., CMP), it appears that few cases of p-DM2 will be missed by utilizing an A1c measurement. ■

Should tiotropium be a maintenance asthma medication?

Source: Peters SP, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-1726.

Traditional maintenance pharmacotherapy for persistent asthma includes inhaled corticosteroids (ICS), leukotriene modulators, and—when used concomitantly with ICS—long-acting beta agonists (LABA). Except for the acute care setting, anticholinergic treatment, like tiotropium (TIO) has been generally thought of as a treatment for COPD rather than asthma.

Peters et al performed a double-blind, crossover trial in asthmatics (n = 210) who were poorly controlled on ICS alone. As add-on treatment, patients were randomized to tiotropium (ICS + TIO), the long-acting beta agonist salmeterol (ICS + LABA), or a doubling of ICS (ICS + ICS).

ICS + TIO was found to be superior to ICS + ICS for morning peak expiratory flow (the primary endpoint of the trial). ICS + TIO was demonstrated to be non-inferior to ICS + LABA for morning peak expiratory flow, prebronchodilator FEV1, and proportion of asthma-controlled days (the secondary endpoint of the trial). These results support the consideration of TIO as a maintenance medication for asthma when used in conjunction with ICS. Because the study duration was brief (14 weeks), the durability of anticholinergic treatment for asthma—for instance, is TIO useful in preventing asthma exacerbations?—remains to be determined. ■

INTERNAL MEDICINE ALERT®

A twice-monthly update of developments in internal and family medicine

Cumulative Index
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