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INSIDE

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MOTIVE-ation!

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *Behavioral therapy works as well as drug treatment for male overactive bladder.*

Source: Burgio KL, et al. Behavioral versus drug treatment for overactive bladder in men: The Male Overactive Bladder Treatment in Veterans (MOTIVE) Trial. *J Am Geriatr Soc* 2011;Nov 7. doi: 10.1111/j.1532-5415.2011.03724.x [Epub ahead of print].

Burgio and colleagues enrolled 203 male veterans (out of 360 assessed for eligibility), attending two VA Medical Centers in Alabama and Georgia, in this randomized, controlled equivalence trial of behavioral therapy (BEH) vs extended-release oxybutynin (OBN) for overactive bladder (OAB). All subjects underwent a clinical evaluation, which included urinalysis, urodynamic testing, post void residual volume (PVR) determination by ultrasound, and kept a voiding diary. They took the alpha-blocker tamsulosin 0.4 mg/d during a 4-week run-in period and continued it throughout the study. Inclusion criteria were self-reported urgency, frequent urination, and > 8 voids/day. Exclusion criteria were recent urological surgery, bed-bound, urine flow rate < 5 mL/s at baseline or < 10 mL/s after run-in, PVR > 250 mL at baseline or > 150 mL after run-in, continuous urine leakage, urinary tract infection, hematuria, fecal impaction, diabetes mellitus in poor control, unstable medical condition, dementia, narrow-angle glaucoma, gastric retention, hypersensitivity to the study drugs, new onset diuretic therapy, and sleep apnea.

The subjects in the behavioral arm were seen by nurse practitioners (NPs) for a comprehensive training program. The NPs taught them how to contract and relax their pelvic floor muscles. They were also instructed on the techniques of delayed voiding and urinary urge sup-

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pression. Nocturia was specifically addressed. The BEH group was told to restrict their fluid intake after 6 p.m. They were taught that if they awoke with the urge to void, they were to lie in bed and try to suppress the urgency by contracting their pelvic floor muscles.

Subjects in the drug-therapy arm were started on extended-release oxybutynin 10 mg daily. The dose was titrated upward or downward at follow-up visits, depending on patient tolerance of side effects and whether PVR was greater than 150 mL, which would trigger a dose reduction.

The trial lasted 10 weeks. The primary outcome was the average number of voids in a 24-hour period. Secondary outcome measures included patient global ratings, ratings of activity restriction, and measures of how disturbing the symptoms and side effects of the treatment were. The subjects were also asked whether they wanted to continue their present therapy or receive another form of treatment.

After the alpha-blocker run-in, 143 of the 203 men who were enrolled continued to have OAB symptoms, 73 randomized to BEH and 70 to OBN. Nineteen subjects dropped out, 9 from BEH and 10 from OBN. The average age of the participants was 64 years (range 42-88), 64% were white, 35% black, and 1% Hispanic. Subjects in BEH reduced their daily voids from an average of 11.3 at baseline to 9.1 at the end of the trial (normal ≤ 8.) Similarly, subjects in the oxybutynin arm reduced their voids from 11.5 to 9.5. Both of these results were statistically significant. Before treatment, subjects in the behavioral arm averaged 2.2 episodes of nocturia per night vs 2.3 for subjects in OBN. Subjects in the behavioral arm had greater reduction in the number of nocturia episodes compared to the drug group (0.7 vs 0.32); this was statistically significant. When the investigators looked at mean urgency scores, OBN subjects had a statistically significant reduction compared to BEH. There was greater patient satisfaction among men in BEH, but this did not reach statistical significance. There were fewer men who complained of bothersome side effects in the behavioral group than the drug therapy group (12.6% vs 28.8%) and fewer wanted to change therapy (29.0% vs 50.0%). Both of these were statistically significant.

■ COMMENTARY

As these investigators define it, OAB is urinary urgency, urge incontinence, frequency, and nocturia. Nocturia, which is often associated with urinary frequency, is defined as an urge to urinate that awakens the person during the night. OAB is usually thought of as a syndrome that afflicts females. However, 17% of males older than 60 years in the United States suffer from it.[1]

Although alpha-blockers commonly are associated with relaxation of the prostatic and bladder neck smooth muscles, they also relax the bladder dome smooth muscle, which accounts for their efficacy in OAB. Antimuscarinic drugs inhibit the muscarinic receptors that mediate normal bladder contractions.[2] The oxybutynin-tamsulosin combination previously has been shown to be more effective than tamsulosin by itself,[3] although, as was shown in the run-in period of this study, tamsulosin by itself was effective for 60 men (30% of those enrolled). Like other antimuscarinic drugs, oxybutynin can cause serious reactions, such as heat stroke and psychosis. However, there are many common reactions (dry mouth, dizziness, constipation, etc.) that are bothersome enough for patients to abandon therapy. Ironically, one of the most common reactions is urinary retention, which is why these investigators were using PVR for monitoring the subjects who were using drug therapy. Normal PVR is less than 100 mL.

Pelvic floor muscle strengthening (also known as Kegel exercises) works on the pubococcygeal muscle and other pelvic diaphragm muscles. Although primarily known as treatment for female stress incontinence, Kegel exercises have also been used in men for incontinence following prostate surgery[4] and for premature ejaculation.[5] To my knowledge, there are no adverse effects of performing Kegel exercises. I suspect that your main problem in prescribing this therapy will be convincing your patient to allow a NP to place a finger into his anus, which is how the NP will teach him to recognize which muscles to contract.

This study raises some questions. It was of brief duration. How long-lasting will the results be? The main limitation of this study was that it was conducted on men who were already taking an alpha-blocker, tamsulosin. Would a different alpha-blocker (terazosin, doxazosin, etc.) work as well?

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Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

Would the results of the study have been the same if the subjects had not been taking an alpha-blocker? The investigators used extended-release oxybutynin with the patients in the drug-therapy arm. Would much cheaper, short-acting oxybutynin have been as effective? What about other antimuscarinic drugs? Extended-release tolterodine in combination with tamsulosin has also been shown to be effective.[6]

The bottom line is this: Medication works for OAB, but behavioral therapy was as good as, if not better than, drug therapy for all outcome measures except urgency. The side effects of BEH are minimal, if not nonexistent. Antimuscarinic drugs have nontrivial side effects. My advice is to recommend BEH and consider an alpha-blocker, unless urgency is your patient's overriding concern and he is willing to put up with the expense and side effects of oxybutynin. ■

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Is Ambulatory BP Monitoring Needed for the Accurate Diagnosis of High BP?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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Dr. Karpman serves on the speakers bureau for Forest Laboratories.

Synopsis: *The use of ambulatory blood pressure (BP) monitoring as a diagnostic strategy for the diagnosis of hypertension after finding an initial raised BP reading in the doctor's office would reduce misdiagnosis. The additional costs of ambulatory monitoring are counterbalanced by cost savings from better targeted therapy and, therefore, ambulatory monitoring is recommended for most patients before the start of antihypertensive drug therapy.*

Source: Lovibond K, et al. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: A modelling study. *Lancet* 2011;378:1219-1230.

HYPERTENSION IS WELL KNOWN AS ONE OF THE KEY RISK FACtors for the development of cardiovascular disease,[1] is a major cause of morbidity and mortality worldwide,[2] and is the most common reason for a primary care referral for consultation among all of the chronic disorders since as many as 25% of adults are hypertensive.[3,4] The diagnosis of hypertension has traditionally been based on the results of one or several BP measurements taken in a physician's office, despite the fact that there are great variations in measurement techniques and the inability to accurately control multiple factors, such as transient anxiety, which may contribute to so-called "white-coat" hypertension.[5-7] Previous studies have demonstrated that ambulatory BP monitoring (ABPM) is more accurate than clinic and home monitoring[8] and have concluded that it should be more frequently utilized.

Lovibond and her colleagues developed a model to assess and compare the cost effectiveness of the three different diagnostic methods (i.e., additional BP measurements in the office, home BP monitoring, ABPM) which are routinely used to evaluate an elevated office BP.[9] They performed a Markov model-based probabilistic cost-effective analysis on a hypothetical primary care population aged 40 years or older who demonstrated a BP measurement greater than 140/90 mmHg and a risk factor prevalence equivalent to the general population. They expressed their findings in terms of costs, quality-adjusted life years, and incremental costs for a quality-adjusted life year gained. Their analysis included the cost of diagnosis, antihypertensive therapy, and the management of associated cardiovascular disease. They concluded that ABPM was more cost-effective when compared with additional office monitoring or home monitoring for confirming the diagnosis of high BP (HBP) in patients with suspected HBP based on a BP measurement of 140/90 mmHg or greater obtained on an initial office or clinic BP measurement.

■ COMMENTARY

ABPM results are known to vary during 24-48 hour measurement periods, but these variations are less than

the variations for home BP monitoring; also, ABPM has been demonstrated to be a better predictor of clinical outcomes than home or office BP measurements.[11] The Lovibond study concluded that ABPM was the most clinically effective, as well as the most cost-effective, diagnostic strategy for confirming the diagnosis of HBP across a range of eight subgroups in both men and women.[9] The study results further concluded that ABPM should be seriously considered for all patients with newly diagnosed hypertension before starting antihypertensive therapy since an accurate diagnosis of true HBP is necessary to determine which patients should receive appropriate drug therapy and which patients should not be treated but simply followed. The relative additional expense of performing ABPM also was demonstrated to be counterbalanced by the cost savings from the better targeting of treatment.

Cost-effectiveness is an increasingly important consideration in all aspects of medical diagnosis and therapy. The Lovibond study was performed primarily to determine the cost-effectiveness of ABPM but the results of the study also clearly demonstrated the medical effectiveness of ABPM technology in evaluating many of the patients that we see on a daily basis. Hopefully, clinicians will be more diligent in the future in their use of ABPM in patients with newly diagnosed presumptive HBP. ■

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What is the Healthiest Systolic Blood Pressure Range for Patients After an Ischemic Stroke?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

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

Synopsis: *A post-stroke analysis of more than 20,000 patients in 35 countries showed that the lowest risk systolic blood pressure (BP) range is 130-139 mmHg. There is a J-shaped curve of risk with an increase in recurrent stroke among patients with a systolic BP below 120 mmHg and above 140 mmHg.*

Source: Ovbiagele B, et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA* 2011;306:2137-2144.

A RANDOMIZED CONTROLLED TRIAL ENROLLED 20,330 PAtients in 35 countries after a non-cardioembolic ischemic stroke to look at the effectiveness of different treatment regimens. The results of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial were published in 2008.[1,2] The trial looked at two antithrombotic regimens (a fixed-dose combination of aspirin with extended-release dipyridamole and clopidogrel) and telmisartan vs placebo. The outcome of the

trial was no difference between the two antithrombotic regimens and no difference between telmisartan and placebo in preventing a second stroke. The mean follow-up period was 2.44 years.

This study is a post hoc observational analysis of all the patients combined as to the rate of recurrent stroke depending on the systolic BP range. The study also looked at a composite of stroke, myocardial infarction, or death from vascular causes. The patients were divided into five groups based on the mean systolic BP level: very low-normal (less than 120 mmHg), low-normal (120-129 mmHg), high-normal (130-139 mmHg), high (140-149 mmHg), and very high (greater than 150 mmHg).

The rate of recurrent stroke was 8% in the very low-normal systolic BP group, 7.2% in the low-normal systolic BP group, 6.8% in the high-normal systolic BP group, 8.7% in the high systolic BP group, and 14.1% in the very high systolic BP group. Similar findings were seen in the secondary analysis of a composite of stroke, myocardial infarction, or death from vascular causes.

■ COMMENTARY

This study confirms a J-shaped curve of risk for systolic BP in patients after an ischemic stroke. While having a high systolic BP over 140 mmHg carries the greatest risk, a systolic BP of less than 120 mmHg is of greater risk than between 120 and 140 mmHg. Interestingly, 130-139 mmHg appears to be the safest range.

Other studies of BP control in different conditions have had inconsistent results, with some showing a J-shaped curve of risk and others not.[3-5] These authors believe that the timing of the studies relative to the time of the first stroke is very important. In this trial, patients were enrolled soon after the first stroke, with almost 40% randomized within 10 days of the index event. This study showed that the greatest risk for recurrent stroke is 3 to 6 months after the previous stroke. Other trials not showing a J-shaped curve of risk enrolled most of their patients more than 1 year and even 5 years after their index event.[6,7]

Blood pressure guidelines are being rewritten to highlight the risk of overtreatment. Unfortunately, we have lived through a period where going as low as possible became the norm and systolic BP above 130 was even regarded as "prehypertension." We already know that low BPs (below 110 mmHg) are dangerous in the elderly. The mean age in this study was 66.1 years and we see that systolic BPs below 120 increase the risk of recurrent stroke. The fact that the 130-139 range was even safer than the 120-129 range should give us pause and alert us that getting below 140 mmHg is the proper treatment goal in treating BP, at least in patients with a previous ischemic stroke, the outcome most associated with high BP. ■

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Pharmacology Update

Zolpidem Tartrate Sublingual Tablets (Intermezzo®) CIV

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

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

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

A LOW-DOSE SUBLINGUAL FORMULATION OF ZOLPIDEM HAS been approved by the FDA for the management of middle-of-the-night (MOTN) awakening. Zolpidem, marketed as Ambien, was originally approved in 1992. The new formulation is marketed by Transcept Pharmaceuticals as Intermezzo.

Indications

Sublingual zolpidem is indicated for as needed use in

the treatment of MOTN awakening followed by difficulty returning to sleep.[1]

Dosage

The recommended dose is 1.75 mg (women) or 3.5 mg (men) given sublingually once per night as needed.[1] The doses are gender specific because women clear the drug at a lower rate then men. Zolpidem should not be taken if there is less than 4 hours remaining before planned awakening.

Zolpidem is available as 1.75 mg and 3.5 mg sublingual tablets.

Potential Advantages

This is the first drug/formulation approved for the indication of MOTN awakening followed by difficulty returning to sleep.

Potential Disadvantages

Sublingual zolpidem shares the same warning and precautions regarding central nervous system depression, abnormal thinking, and behavioral changes as regular strength zolpidem, as well as other sedative-hypnotics. Behaviors may include "sleep-driving," preparing and eating food, making phone calls, etc.

Comments

Zolpidem tartrate has been formulated as a sublingual tablet for disintegration and absorption via the oral mucosa. The safety and efficacy was studied in two randomized, double-blind, placebo-controlled studies.[1,2] Study one was based on scheduled dosing (n = 82) and study two was based on as-needed dosing (n = 295). Study one was a randomized, double-blind, placebo-controlled, three-way crossover study in adult subjects with DSM-IV primary insomnia and polysomnography and sleep diary confirmed MOTN awakening.[2] Subjects were required to have MOTN awakening characterized by at least three awakenings per week and needing at least 30 minutes to fall back to sleep. Each subject received three 2-night treatment periods of 1.75 mg, 3.5 mg, and placebo with a 5-to-12-day washout period. The primary efficacy endpoint was mean latency to persistent sleep (LPS) following MOTN awakening comparing 3.5 mg and placebo. Secondary endpoints included total sleep time (TST), subjects' rating of quality of sleep, safety as assessed by adverse events, vital signs, laboratory parameters, and next morning residual effects. At each treatment night, subjects were awakened 4 hours after initial lights out regardless of the sleep stage. LPS values were 28.1, 16.9, and 9.7 minutes, respectively, for placebo, 1.75 mg, and 3.5 mg of sublingual zolpidem. Sleep onset was significantly faster with both active doses compared to placebo and 3.5 mg was faster than 1.75 mg. TST values were 183, 198, and 209 minutes with similar statistical differences. Zolpidem 3.5 mg showed the best improvement in sleep quality. Next-morning residual effects and adverse events were not significantly different between zolpidem and placebo.

In the second study where sublingual zolpidem (3.5 mg) or placebo was given on an as-needed basis, zolpidem showed a significantly shorter patient-estimated time to fall back to sleep after MOTN awakening.[1] The daytime pharmacodynamics and pharmacokinetics of sublingual zolpidem were assessed in a single-dose, randomized, double-blind, placebo-controlled, crossover study.[3] Three doses (1 mg, 1.75 mg, and 3.5 mg) were compared to placebo. Subjects were randomized to dosing sequences that included four treatments separated by 5-12 days. Treatment was given approximately 1 hour after awakening and assessed over 5 hours. Daytime sedation was assessed objectively by the Digit Symbol Substitution Test and subjectively by the Visual Analog Scale. Blood levels of zolpidem were measured up to 12 hours post-dose. Significant sedation was evident in 20 minutes and lasted up to 90 minutes for the 3.5 mg dose. There was no difference among the treatments 4-5 hours post dose. Subjective self-rated significant sedation for the 1.75 mg and 3.5 mg doses compared to placebo was from 20 minutes through 2 hours. Pharmacodynamics seem to mirror the pharmacokinetics as plasma levels above 20 -25 ng/mL were reached within 20 minutes and maintained for up to 4 hours.

Clinical Implications

Insomnia is a common disorder characterized by difficulty falling asleep, maintaining sleep, or early morning awakening.[4] More than a third of adults experience MOTN awakening three or more nights per week.[2] Previously approved medications for insomnia are directed at sleep initiation and maintenance. A zolpidem tartrate sublingual tablet is the first drug approved for MOTN awakening. ■

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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.

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To earn credit for this activity, follow these instructions:

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CME Questions

1. Your elderly male patient complains of symptoms of an overactive bladder. Based on the Burgio et al study, what can you advise him?

a. Drug therapy results in greater reduction of nocturia than behavioral therapy.
b. Behavioral therapy has more adverse side effects than drug therapy.
c. Behavioral therapy works better than drug therapy at reducing urgency.
d. He will be less likely to stop drug therapy than behavioral therapy.
e. Behavioral therapy works as well as drug therapy for reducing the number of voids per day.

2. Ambulatory blood pressure monitoring:

a. is too costly to be used on most patients.
b. should be considered for most patients demonstrating an initial elevated blood pressure reading in the office before starting antihypertensive therapy.
c. does not correlate better than office blood pressure readings with cardiovascular outcomes.
d. is not cost-effective in the treatment of patients with hypertension.

3. What is the lowest risk range for systolic blood pressure after an ischemic stroke?

a. Less than 120 mmHg
b. 120-129 mmHg
c. 130-139 mmHg
d. 140-149 mmHg
e. Above 150 mmHg

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

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

What Factors Lead to Acquisition of *Clostridium difficile*?

Source: Loo VG, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med* 2011;365:1693-1703.

The toxicity associated with intestinal habitation by *Clostridium difficile* ranges from asymptomatic colonization to life-threatening infection. In the United States, *C. difficile* is the most common cause of health care-associated diarrhea. Although the association of *C. difficile* with use of antibiotics and/or hospitalization is clear and well established, why certain individuals fall prey to infection/colonization — whereas most do not — remains ill-defined.

Loo et al performed a prospective study of patients admitted to Canadian hospitals over 15 months (n = 4143). Subsequent to hospital admission, *C. difficile* infection was identified in 2.8% (n = 117) and colonization in 3% (n = 123); excluded from these numbers were the 4.4% of individuals who were already *C. difficile* colonized upon admission.

As has been noted in previous observational studies, older age, antibiotic use, and use of proton pump inhibitors (PPI) or histamine-type 2-receptor antagonists (H2RA) were each associated with *C. difficile* colonization and infection. The mechanism by which PPI/H2RA use is associated with *C. difficile* remains speculative, but is attributed to disturbance of bacterial flora. Whether more restraint in use of antibiotics, PPI, or H2RA medications will reduce the incidence of serious *C. difficile* infections remains to be determined. ■

The Relationship Between Sleep and Hypertension

Source: Bansil P, et al. Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: Results from the National Health and Nutrition Examination Survey, 2005 to 2008. *J Clin Hypertens* 2011;13:739-743.

It is probably obstructive sleep apnea (OSA) with which clinicians most familiarly associate hypertension (HTN). Indeed, some recent trials have found a remarkably high prevalence of previously unsuspected OSA in persons with resistant HTN. What about other sleep variances, such as persons with sleep movement disorders (e.g., restless legs, sleep apnea), short sleep (< 7 hrs/night), or poor sleep? The authors report on data obtained through the most recent National Health and Nutrition Examination Survey obtained through direct interview with 10,308 adults.

Overall, persons with HTN were statistically significantly more likely to have a sleep disorder than normotensive individuals (11% vs 6%). "Poor sleep" did not appear to be a relevant factor, but less than 7 hours of sleep nightly was. No gender or ethnicity differences were detected.

In contrast to prior data sets, this study did not find a consistent relationship specifically between sleep disorders and HTN. Rather, it was in persons who reported both a sleep disorder and short sleep that risk of HTN rose steeply: this combination was associated with more than a doubling of risk. Finally, the authors also note that more than two-thirds of persons with sleep problems had not discussed their issues with a health professional. ■

DPP4 Inhibitors are Associated with Reduced Risk of Hip Fracture

Source: Monami M, et al. Dipeptidyl peptidase-4 inhibitors and bone fractures: A meta-analysis of randomized clinical trials. *Diabetes Care* 2011; 34:2474-2476.

In an era where concern about adverse consequences of pharmacotherapy on bone health are prominent — proton pump inhibitors associated with increased risk of hip fracture, bisphosphonates associated with an increased risk of spiral femoral fractures, and even thiazolidinediones noted to increase fracture risk — a more sanguine headline is certainly welcome.

The dipeptidyl peptidase-4 inhibitors (DPP-4) currently include three agents: sitagliptin, saxagliptin, and linagliptin, each of which provides a fairly similar degree of glucose reduction. The physiologic activity of GLP-1 (the primary pathway through which DPP-4 treatment enhances glucose control) includes activation of osteoblasts and inhibition of osteoclasts. Animal studies have shown that DPP-4 agents actually increase bone density, but no large, long-term clinical trial has confirmed a relationship between DPP-4 and fractures in humans.

Monami et al performed a meta-analysis on trials of DPP-4 inhibitors lasting 6 months or longer from which data on fractures was able to be extracted. Based on 28 trials of DPP-4 treatment (n = 11,880) vs comparator (n = 9175), the odds ratio for fracture was 40% less in persons receiving DPP-4 than in comparator. DPP-4 appear to have a protective effect on bone. ■

In Future Issues:

CPAP for the Metabolic Syndrome in Patients with Obstructive Sleep Apnea