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INSIDE

Morning Headache—Prevalence and Risk Factors

ABSTRACT & COMMENTARY

Synopsis: *Although long thought to be indicative of sleep disorders, morning headache has many diverse risk factors. It is a common disorder.*

Source: Ohayon MM. *Arch Intern Med*. 2004;164:97-102.

Sleep and headache have a long and complex relationship.[1] Morning (or awakening) headache has been linked to sleep disorders,[2] especially obstructive sleep apnea syndrome, but this association is controversial.[3] Other associations include bruxism, periodic limb disorders, hypertension, and living with heavy snorers. Ohayon set out to determine the prevalence of morning headache in the general population and to look for correlates among 5 categories of factors (sociodemographic determinants, use of psychoactive substances, organic diseases, sleep disorders, and mental disorders).

Using a sophisticated, computerized telephone script, this study contacted 18,980 people, 15 years or older, living in the United Kingdom, Germany, Italy, Portugal, and Spain between 1994 and 1999. Women comprised 51.3% of the population. People were excluded who could not speak the national language, had a hearing or speech impairment, or had an illness that precluded an interview. There was no attempt to classify the morning headaches into migraine, tension, cluster, or cervicogenic.

Of these participants, 1442 (7.6%) had morning headaches, and 1.3% reported daily morning headaches. On multivariate analysis the following variables were statistically significant: age younger than 25 years or between 45 and 54, female gender, unemployed or homemaker, musculoskeletal disease, hypertension, heavy alcohol consumption (6 drinks/d), use of anxiolytic medication, nightmares of any frequency, insomnia, circadian rhythm disorder, sleep-related breathing disorder, dysomnia NOS (which includes restless leg syndrome and periodic limb movement disorder), loud snoring, anxiety, major depressive disorder with or without anxiety, and stress. Coffee or tobacco consumption, use of antidepressant or hypnotic medica-

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tion, heart disease, upper airway disease, and other nonpainful diseases were not significant. When the analysis was limited to individuals with daily morning headaches, only hypertension, musculoskeletal disease, heavy alcohol consumption, use of anxiolytics, nightmares = 1 night/week, insomnia, circadian rhythm disorder, sleep-related breathing disorder, dysomnia NOS, and major depressive disorder with or without anxiety remained significant. Individuals with morning headache were more apt to report feeling anxious depressed, inefficient, irritable, fatigued, and overly sensitive to light, touch, and sound during the daytime.

COMMENT BY ALLAN J. WILKE, MD

A prevalence of 7.6% works out to 1 in 13 people, making morning headache very common. As this study demonstrates, it is not limited to sleep disorders. It is tempting to try to find a "final common pathway" that links these risk factors. For instance, hypoxia could reasonably account for headaches. Obstructive sleep apnea and use of alcohol and psychoactive drugs (through their depressant effects on the respiratory system) could cause hypoxia. However, nighttime duration of hypoxia has not been shown to be associated with morning headache.[4] Anything that might disturb sleep (pain from a musculoskeletal disorder, insomnia, nightmares, dysomnia, etc) could cause headaches secondary to sleep deprivation.[5,6] Other studies have confirmed the association between mood disorders and morning headaches,[7] but not all patients with morning headache have a mood disorder. This study did not ask whether the subject was sleeping with someone who was a loud snorer, although you may surmise this based on the increased numbers of females and homemakers with morning headache. A previous study demonstrated disturbed sleep, morning headache, and daytime sleepiness among women living with a snoring spouse.[8] This phenomenon was discussed in Internal Medicine Alert earlier this year.[9] There does not appear to be a unifying theme; it is likely that morning headache is a multifactorial syndrome. ■

References

1. Dodick DW, et al. *Headache*. 2003;43:282-292.
2. Jennum P, Jensen R. *Sleep Med Rev*. 2002;6:471-479.
3. Jensen R, et al. *Acta Neurol Scand*. 2004;109:180-184.
4. Greenough GP, et al. *Sleep Med*. 2002;3:361-364.
5. Blau JN. *Cephalalgia*. 1990;10:157-160.
6. Spierings EL, et al. *Headache*. 2001;41:554-558.
7. Neau JP, et al. *Cephalalgia*. 2002;22:333-339.
8. Ulfberg J, et al. *Health Care Women Int*. 2000;21:81-90.
9. Phillips BA. *Internal Medicine Alert*. 2004;26:10-11.

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More Hazards of Air Travel

ABSTRACT & COMMENTARY

Synopsis: *There is an association between long-distance air flights and venous thromboembolism, but the role of traditional risk factors and prophylactic measures requires more study.*

Source: Hughes RJ, et al. *Lancet*. 2003;362:2039-2044.

VIRCHOW HYPOTHESIZED THAT BLOOD STASIS IS AN important factor in venous thrombosis, and it

undoubtedly is a major factor in the observed association between air travel and venous thromboembolism. However, the importance of other risk factors and the precise frequency of air travel-related thromboembolism are uncertain. Thus, Hughes and colleagues in New Zealand took advantage of their geographic isolation to study this problem by enrolling volunteers traveling at least 4 hours by air who were going to return within 6 weeks. Excluded were those with previous venous thromboembolism, on anticoagulants, post-major surgery within 6 weeks, with cancer within 6 months, with renal insufficiency, or pregnant. Enrollment stopped at 1000 subjects. All had baseline D-dimer studies, and 83 were excluded because of elevated values. Another 39 failed to return for their follow-up visit, leaving a total study population of 878. All subjects were evaluated clinically and told to keep a diary about their pre-, post-, and in-flight activities. Upon return they were contacted within 72 hours for blood work including D-dimer, thrombophilic risk factors, and anticardiolipin antibodies. D-dimers were repeated at 2 weeks and 3 months after travel, and any positive values or symptoms suggestive of venous thrombosis were evaluated further by lower extremity ultrasonography, pulmonary CT angiography, or ventilation perfusion scintigraphy.

The frequency of confirmed venous thromboembolism (VTE) was 1% (9/878)—4 with pulmonary emboli, 3 with proximal, and 2 with distal lower limb deep venous thrombosis. The mean total duration of air travel was 39 hours, most of which was in economy class (about 80%). With total air travel of ≤ 24 hours, 10% of subjects used compression stockings and when total air travel exceeded 24 hours, 18% did. Of the 112 subjects who were evaluated for venous thromboembolism, 76 were studied on initial return contact, 30 at 2 weeks, and 8 at 30 days. All of the subjects with confirmed VTE had a positive D-dimer at the initial review; 6 had risk factors for VTE pre-travel; 2 had thrombophilic abnormalities discovered in the post-travel testing; 2 traveled exclusively in business class; 5 used aspirin; and 4 wore compressive stockings. When those with VTE were compared to those without, there was no difference in length of travel (42 vs 39 hours), but no one with a total travel duration < 24 hours had VTE. Hughes et al concluded that there is an association between long-distance air flights and VTE, but the role of traditional risk factors and prophylactic measures requires more study.

COMMENT BY MICHAEL H. CRAWFORD, MD

The major finding of this study is that long-duration air travel is associated with VTE even in patients with low to moderate risk, since high-risk patients were excluded. VTE was associated with total flight durations > 24 hours. Since the longest flight known from New Zealand is 14 hours, risk was associated with multiple flights within the 6-week window of the study. Since patients were studied when they returned, Hughes et al do not know which flight was the culprit. Two subjects were evaluated after outward flights because of symptoms suggesting VTE, but neither had VTE confirmed. Thus, their data suggest that most VTE events occur after multiple flights within 6 weeks, usually after return from the trip.

The value of prophylactic measures was difficult to determine. One in 6 subjects used compressive stockings and almost one-third were on aspirin, which suggests that the study group may have been better informed than the more general flying public about the risks of VTE. Thus, the incidence of 1% in this study may have been an underestimate of the risk of VTE with total air travel > 24 hours. Also, the value of in-flight exercise, hydration, avoidance of alcohol, and other popular prophylactic measures could not be determined. However, some patients with documented VTE did use compressive stockings and aspirin and flew business class, so it is unlikely that these 3 measures are completely preventative. The only sure-fire preventative strategy was to not take air trips lasting > 24 hours total. ■

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

Cost-Effectiveness of Influenza Treatment

Synopsis: *For unvaccinated or high-risk vaccinated patients during the influenza season, empirical oseltamivir treatment is cost-effective. For other patients, rapid diagnostic testing followed by treatment with oseltamivir is cost-effective. Empirical amantadine treatment offers a low-cost alternative if patients cannot afford oseltamivir*

Source: Rothberg MB, et al. *Ann Intern Med*. 2003;139: 321-329.

Using decision analysis, the cost-effectiveness of rapid diagnostic testing and antiviral therapy for influenza-like illness was evaluated in older adults (older than 65). The model was based on several key assumptions, including that neuraminidase inhibitors would

decrease hospitalizations by 33%, along with a comparable reduction in complications and antibiotic use, although zanamivir would be somewhat less effective than oseltamivir because ~50% of older adults would have difficulty loading and administering the medication. In addition, it was assumed that amantadine and rimantadine were less effective because they would not reduce hospitalization and are only effective against influenza A virus. The model was not sensitive to the prevalence or severity of medication side effects.

Not surprisingly, in adults at greatest risk for influenza—unvaccinated, institutionalized, nursing home residents, etc—empiric treatment with oseltamivir without diagnostic testing was the most cost-effective strategy. In patients at lower risk (eg, those who have been vaccinated), rapid diagnostic testing followed by appropriate therapy with oseltamivir was the most cost-effective approach. Empirical amantadine was less cost effective in either circumstance, but could be used if patients had to pay for drug out of their own pocket and couldn't afford the more expensive agent. (This sounds a bit like backward logic to me: Oseltamivir is cost-effective as long as someone else is paying for it?)

COMMENT BY CAROL A. KEMPER, MD

While these conclusions largely make sense, one wonders how the model would perform in the current year when the predominant circulating strain of influenza virus (eg, A/Fujian/411/2002) is not included in (although may be partially covered by) the current vaccine. ■

Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Palo Alto, Calif.

Do Isolation Precautions for MRSA Compromise Patient Care?

ABSTRACT & COMMENTARY

Synopsis: *As determined by process-of-care measurement, adverse event occurrence, and patient satisfaction, quality of care is compromised by infection control procedures.*

Source: Stelfox HT, et al. *JAMA*. 2003;290:1899-1905.

To determine whether isolation procedures used for control of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals might affect patient safety, Stelfox and associates retrospectively reviewed data from 2 large, urban teaching hospitals: Sunnybrook and Women's College Health Sciences Centre in Toronto and Brigham and Women's Hospital in Boston.

Stelfox et al analyzed 2 sets of patients: a consecutive series of adults admitted to the Toronto hospital for a 1-year period and a series of adult patients consecutively admitted to the Boston hospital during a 3.5-year period with a diagnosis of congestive heart failure (CHF). The latter group was studied because established standards of care relating to management of CHF facilitated an objective measurement of quality of care. In each series, patients who were managed with contact precautions, as specified by Centers for Diseases Control and Prevention guidelines, were matched to controls (2 control patients for each isolated patient) by identifying patients who occupied each isolated patient's hospital bed immediately before and immediately after the isolated patient. Isolated patients were either colonized (in 96% of cases) or infected (in 4%) with MRSA.

Safety was assessed by 3 criteria: process of care, adverse events, and patient satisfaction. Process of care was a surrogate for thoroughness of care and included indicators such as vital sign recording, presence or absence of nurses' and physicians' notes, and in the CHF cohort, whether left ventricular function and ejection fraction were evaluated, whether education efforts were documented, and if follow-up appointments were scheduled. Adverse events served as a marker for outcomes of care and included injuries that lengthened hospital stay, produced disability, or resulted in abnormal laboratory test results. Patient satisfaction was assessed by identifying instances of patients' leaving against medical advice, complaints about medical care, and altercations or suicide attempts.

The results? Isolated patients received a lower level of care, as reflected in vital sign deficiencies, absence of nurses' and physicians' notes, documentation of patient education and follow-up appointment scheduling, and differences in medications prescribed upon hospital discharge. In addition, isolated patients had an increased incidence of such adverse events as falls, pressure ulcers, and fluid and electrolyte disorders. Patient satisfaction was much lower in isolated patients than in controls (isolated patients were 23 times more likely to have lodged a complaint).

No differences in hospital mortality were observed.

COMMENT BY JERRY D. SMILACK, MD

This sobering, provocative report raises important questions that are infrequently asked whenever isolation procedures are instituted. In our quest to limit transmis-

sion of infections to patients and to ourselves, do we inadvertently reduce the level of care to isolated patients? What is the psychological effect of isolation on patients and their visitors?

Others[1,2] have noted that health care worker contact with patients is reduced when isolation precautions are imposed. In the present study, Stelfox et al have carefully documented serious safety and medical care deficiencies associated with isolation precautions for MRSA. Since data were gathered primarily by retrospective chart review—with its attendant reliance on documentation—one might wonder what additional deficiencies would have been observed had concurrent review been in place.

Stelfox et al correctly call for further studies to determine whether certain components of isolation procedures might be more important for control of infection but less deleterious than others. They also wonder whether their findings apply to hospitals of smaller sizes or different locales. ■

Dr. Smilack is Infectious Disease Consultant, Mayo Clinic Scottsdale, Scottsdale, Ariz.

References

1. Kirkland KB, et al. *Lancet*. 1999;354:1177-1178.
2. Higgins L, et al. *J Gen Intern Med*. 2001; 16(suppl 1):200. Abstract.

Long-Term Outcome Comparison of Coronary Angioplasty vs Standard Medical Therapy

ABSTRACT & COMMENTARY

Synopsis: *It appears safe to conclude that patients with mild-to-moderate angina can be safely managed with continued medical therapy, but percutaneous coronary intervention is certainly indicated and appropriate if anginal symptoms are not controlled by maximum, aggressive medical management.*

Source: Henderson RA, et al. *J Amer Coll Cardiol*. 2003;42: 1161-1170.

THE OPTIONS FOR TREATING PATIENTS WITH ANGINA pectoris include carefully regulated anti-anginal medications, percutaneous coronary intervention (PCI), or coronary artery bypass surgery (CABG). Randomized clinical trials[1-3] suggest that PCI is slightly less effective at relieving angina than CABG, but neither revascularization strategy provides a prognostic advantage in the majority of patients. Several smaller trials have compared the PCI approach with the results obtained by a variety of medical treatment strategies, but most have reported only limited follow-up data.[4-8]

Henderson and colleagues designed the second Randomized Intervention Treatment of Angina (RITA-2) trial to compare the long-term results of percutaneous transluminal angioplasty (PTCA) vs medical therapy in 1018 patients considered suitable for either treatment. The primary trial end point was the 5-year rate of death or nonfatal myocardial infarction (MI). The initial strategy of PTCA was found not to influence the risk of death or MI but it did improve angina and exercise tolerance. Henderson et al concluded that patients with angina pectoris who were considered suitable for PTCA or medical therapy can be safely managed with continued medical therapy alone however, PTCA is appropriate if symptoms are not controlled medically.

■ COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

The RITA-2 trial results provide the only currently available randomized evidence comparing the long-term consequences of PCI vs medical treatment in patients with angina pectoris. The extensive follow-up for a median 7-year period reported in this article clearly demonstrated that the initial policies of PTCA and medical therapy in patients considered suitable for either treatment are comparable with respect to death and nonfatal MI but that an initial policy of PTCA was associated with a lower prevalence of subsequent angina and with improved exercise tolerance. It should be clearly recognized that medical management initially consisted only of appropriate antianginal (ie, usually a beta-adrenoceptor blocker with a calcium antagonist and/or with long-acting nitrates) therapy for symptom relief. Also, it should be noted that there was a substantial initial reduction in anginal symptoms in patients randomized to PTCA compared with patients assigned medical therapy but that this treatment difference attenuated with the passage of time. The most powerful predictors of symptomatic status at 5 years were the presence of restlessness, the exercise time, and the angina grade at baseline.

The RITA-2 trial enrolled patients from 1992 through 1996, and, of course, there have been significant advances in both medical (ie, use of clopidogrel, glycoprotein IIb/IIIa receptor antagonists, etc) and interventional treatment (ie, increased use of coronary stents, availability of drug-coated stents, etc). It is therefore important to recognize the relatively limited value of the

RITA-2 trial results, which deserve to be updated with new long-term studies comparing current PCI interventional therapy with modern medical treatment. However, it appears safe to conclude that patients with mild-to-moderate angina can be safely managed with continued medical therapy, but the PCI approach is certainly indicated and appropriate if anginal symptoms are not controlled by maximal, aggressive medical management. ■

References

1. Henderson RA, et al. *Lancet*. 1998;352:1419-1425.
2. BARI Investigators. *J Am Coll Cardiol*. 2000;35: 1122-1129.
3. King SB, et al. *J Am Coll Cardiol*. 2000;35:1116-1121.
4. Folland ED, et al. *J Amer Coll Cardiol*. 1997;29: 1505-1511.
5. Hartigan PM, et al. *Am J Cardiol*. 1998;82:1445-1450.
6. Hueb WA, et al. *Circulation*. 1999;100(Suppl 2): 107-113.
7. Pitt B, et al. *N Engl J Med*. 1999;341:70-76.
8. Dakik HA, et al. *Circulation*. 1998;98:2017-2023.

Pharmacology Update

Tiotropium Bromide Inhalation Powder (Spiriva)

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

THE FDA HAS APPROVED THE FIRST ONCE-DAILY, QUATERNARY ammonium, anticholinergic bronchodilator for the treatment of chronic obstructive pulmonary disease (COPD). Tiotropium is 10-fold more potent than ipratropium bromide and has a much longer duration of action.[1] It is manufactured by Boehringer Ingelheim Pharmaceuticals, Inc and co-marketed by Boehringer Ingelheim and Pfizer as Spiriva.

Indications

Tiotropium is indicated for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.[2]

Dosage

The recommended dose is 1 capsule inhaled once daily with the HandiHaler inhalation device. Each capsule contains 18 µg of tiotropium. No dosage adjustment is needed in patients with renal or hepatic impairment, although patients with moderate-to-severe renal impairment should be monitored closely.[2]

Potential Advantages

Tioprotium is administered once daily compared to 4 times a day for ipratropium. Trough pulmonary function with tiotropium (ie, mean predose morning FEV_1), the primary end point, was statistically superior to ipratropium (administered 4 times a day) and salmeterol (administered twice daily).[1,3,5]

Potential Disadvantages

Dry mouth is the most common side effect, and the frequency is higher than with ipratropium (12.1% vs 6.1%).[3] This was more common in older patients and in women.[7] Other side effects include urinary effects and constipation. A higher percent of patients on tiotropium compared to ipratropium had "marked" elevation of LDH.[7]

Comments

Tiotropium is the first quaternary ammonium anticholinergic drug approved since ipratropium. It has similar affinity for the muscarinc receptor subtypes, M1, M2, and M3. However, its slow dissociation (about 100 times more slowly than ipratropium) from M1 and M3 contributes to its long duration of action.[1] Six phase III studies supported the approval of the drug. Four were 1-year studies (2 US and 2 European), and 2 were 6-month multinational studies.[3-7] The combined study population was 2663—1308 randomized to tiotropium and the rest to placebo or active control (ipratropium or salmeterol). Patients had relatively stable COPD with $FEV_1 \leq 60\%$-65% of predicted, FVC ≤ 70%, at least 40 years of age, and a smoking history of > 10 pack-years. The primary end point was change from baseline in mean morning predose FEV_1 value. Other end points included health-related quality-of-life instruments (St. George's Respiratory Questionnaire and SF36), COPD exacerbation, COPD hospitalization, and dyspnea. As expected based on its duration of action, tiotropium showed statistically significant improvement in mean morning predose FEV_1 compared to placebo and active controls. The mean difference in trough FEV_1 response ranged from 110 to 180 mL. Mean peak response ranged from 250 to 310 mL.[7] In 1 of the 2 comparative studies tiotropium showed a reduction in the rate of COPD exacerbation compared ipratropium although the published combined results favored tiotropium.[3,7] A similar pattern was seen with 2 placebo-controlled studies.[5,7] In general, there was no clear, consistent, clinical superiority in terms of the other end points over comparators such as ipratropium or salmeterol,

although some numerical advantages were noted. Tiotropium appears to be well tolerated, and tachyphylaxis was not evident in 1-year studies.[1] Boehringer Ingelheim also sought an indication for the relief of dypsnea related to COPD. However, the FDA concluded that data did not support this proposed indication.[7] Tiotropium is expected to be available mid-year. Cost is not available at this time.

Clinical Implications

COPD affects more than 5% of the adult population, and its mortality and morbidity is increasing.[8] Bronchodilators are standard pharmacological therapy. These include short- and long-acting beta agonists and short-acting anticholinergic. The introduction of tiotropium offers a long-acting anticholinergic bronchodilator with more convenient dosing. ■

References

1. Hvizdos KM, Goa Kl. *Drugs*. 2002;62(8):1195-1203.
2. Spiriva® Product Information. Boehringer Ingelheim Pharmaceutical Inc, February 2004.
3. Vincken W, et al. *Eur Respir J*. 2002;19(2):209-216.
4. Donohue JF, et al. *Chest*. 2002;122(1):47-55.
5. Brusasco V, et al. *Thorax*. 2003;58:399-404.
6. Tashkin D, Kesten S. *Chest*. 2003;123:1441-1449.
7. www.fda.gov/ohrms/dockets/ac/02/briefing/3890B1_05_Clinical%20Briefing.pdf
8. Sin DD, et al. *JAMA*. 2003;290(17):2301-2312.

CME Questions

8. Which one of the following statements is true? In patients with angina pectoris who are considered suitable for PTCA or medical therapy:

a. they can be safely managed with continued medical therapy alone.
b. PTCA is never an appropriate form of therapy.
c. initial therapy with PTCA does not improve angina or exercise tolerance.
d. the risk of death is diminished if PTCA is the initial treatment strategy.

9. On multivariate analysis, all of the following risk factors for morning headache *except* which one were statistically significant?

a. coffee consumption
b. female gender
c. heavy alcohol consumption
d. major depressive disorder
e. hypertension

Answer: 8 (a); 9 (a)

By Louis Kuritzky, MD

Risk of Adenocarcinoma in Barrett's Esophagus

ALTHOUGH SURVEILLANCE OF BARrett's esophagus (BES) for early detection of esophageal adenocarcinoma (E-CA) has become routine, the cost efficacy of this intervention is only scantily described.

Population data from Northern Ireland include all incident cancers. Murray and colleagues identified all subjects who had undergone esophageal biopsies with a diagnosis of BES between 1993 and 1999 and followed them up until 2000 identifying the number of subjects who were ultimately diagnosed with E-CA. Subjects who were diagnosed with E-CA within 6 months of the initial biopsy were not included in the data analysis.

Of 15,670 esophageal biopsies, almost 3000 met criteria for BES. In a follow-up period of 3.7 years (range, 1-8 years) 29 E-CA cases were identified. The mean yearly rate for E-CA was 0.26%, and 2.5 times higher in men than women. Risk was greatest in men older than 70 with specialized intestinal metaplasia found at esophageal biopsy, in whom the annual incidence was > 1%. Murray et al comment that when E-CA annual risk is 1%, surveillance may be cost-effective but that based upon these data, restricting surveillance to only the "high-risk" population would miss two-thirds of the incident cases of cancer. Our knowledge about the optimum schedule for BES surveillance remains incomplete. ■

Murray L, et al. BMJ(USA). 2003;3: 534-535.

Long-Term Effect of Doxazosin, Finasteride, and Combination for BPH

BENIGN PROSTATIC HYPERPLASIA (BPH) is commonly treated with alpha blockers such as doxazosin (DOX), alpha reductase inhibitors such as finasteride (FIN), or both. Long-term trials of DOX and FIN in combination have not been previously available to allow clinicians to compare the effect of alpha blockers, alpha reductase inhibitors, or both upon BPH symptoms. In addition to the value of symptom control, long-term treatments that reduce the need for surgical intervention are desired by clinicians and patients alike. Previous trials of alpha reductase inhibitors alone have indicated success in reducing the need for surgical intervention and the frequency of acute urinary retention.

Approximately 3000 men with symptomatic BPH who had not previously undergone surgical intervention, and whose PSA was < 10, were randomized to placebo, DOX, FIN, or DOX + FIN. The primary outcome was the first occurrence of a meaningful increase in the AUA symptom score (4 points or greater on a scale of 30).

Compared to placebo, both FIN and DOX had a statistically significant effect on the AUA symptom score (34-39% risk reduction). For this same end point, the benefit of combination therapy (DOX + FIN) was significantly greater than either agent alone. The risk of required surgical intervention or acute urinary retention was significantly reduced by FIN and DOX + FIN, but not DOX alone. Clinicians now have multiple logical options for long-term treatment of BPH. ■

McConnell JD, et al. N Engl J Med. 2003;349:2387-2398.

Once Daily Valacyclovir to Reduce Herpes Transmission

AMONG GENITAL HERPES VIRUS (HSV-2) discordant couples, couples in whom one partner is HSV-2 infected and the other has not been, several strategies have been used to reduce likelihood of transmission to the uninfected partner. None of the strategies, save abstinence, can provide perfect assurance that HSV-2 transmission will not occur.

Asymptomatic persons shed HSV-2 and place their sexual partners at risk of transmission even during asymptomatic periods. It has been reported that subclinical viral shedding is the primary source of HSV-2 transmission. Antiviral treatment can reduce both the amount of time subclinical viral shedding occurs and the intensity with which virus is shed.

HSV-2 discordant monogamous couples (n = 743) were randomized to 500 mg valacyclovir QD (VAL) vs placebo for 8 months.

Only 4 of 743 susceptible partners on VAL developed symptomatic infection during the study period, compared with 16 placebo recipients (hazard ratio = = .25). Similarly, seroconversion was found in 14 of 743 VAL-treated susceptibles, vs 27 of 741 on placebo. Placebo-treated patients excreted HSV-2 on 10.8% of days, compared with 2.9% of days with VAL treatment.

Once-daily VAL can reduce, but not eliminate, HSV-2 transmission. ■

Corey L, et al. N Engl J Med. 2004;350(1):11-20.

In Future Issues: **Can We Reduce the Incidence of Diabetes?**