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## INSIDE



# Today's Therapeutic Options for Hot Flashes

ABSTRACT & COMMENTARY

***Synopsis:*** *Since the results of the Women's Health Initiative randomized trials, many fewer postmenopausal women are using estrogen to control hot flashes. Alternatives include progesterones, antidepressants in low doses, caffeine avoidance, exercise, phytoestrogens, and black cohosh. More studies are needed to clarify the benefits of these therapies.*

**Source:** Pradhan A, Bachmann G. *Women's Health in Primary Care*. 2003;6(11):527-534.

MANY FEWER WOMEN WISH TO TAKE ESTROGEN AFTER THE results of the Women's Health Initiative randomized trials showing increased risk of heart disease and cancer. This leaves the control of troublesome hot flashes after menopause to other methods, most of which are not as effective. This review by 2 leaders in women's health at the Robert Wood Johnson medical school clarifies the data supporting other methods.

A hot flash is the sudden onset of an increase in body temperature that induces feelings of warmth, reddening of the skin in the upper body and perspiration. In most menopausal women, these symptoms last for 1-2 years, but 25% of women experience vasomotor symptoms for more than 5 years. These symptoms are clearly related to a decline in estrogen production, and hence estrogen replacement is the most effective treatment.

Several placebo-controlled studies have shown that progesterones alone may alleviate the symptoms. Oral doses of medroxyprogesterone acetate of 10-20 mg/d can be 50% to 80% effective. At these doses, side effects of irregular bleeding, fatigue, mood changes, bloating and weight gain do occur. This makes nonhormonal alternatives more attractive.

Two of the newer antidepressants—paroxetine and venlafaxine—have been shown in low doses to reduce vasomotor symptoms by about 60%. They offer the best pharmacologic option for treatment. Older drugs such as bellergal, clonidine patch, and methyldopa are either not effective or have side effects exceeding the benefit to warrant their use.

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Lifestyle methods worth trying include avoidance of spicy foods, caffeine, and alcohol. Dressing in layers and lightweight clothing help prepare the women to minimize the discomfort. Exercise is beneficial in reducing vasomotor instability. Of all of the "natural" methods suggested for hot flashes, phytoestrogens, such as from soy and other legumes, and black cohosh have some evidence to support their use. Phytoestrogens are best consumed by diet rather than in pills. A nice review of black cohosh was recently published in the American Family Physician (July 1, 2003 http://www.aafp.org/afp/20030701/114.html).

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

The variation among menopausal and postmenopausal women with respect to hot flashes is great, and treatment must be individualized. The temporary nature of this problem needs to be kept in mind, since many women consider that this problem will follow them into their sixties. Pradham and Bachmann point out that the WHI cohort consisted mostly of older women (mean age, 62) while those who typically seek help for hot flashes are younger (mean age, 51). When the vasomotor symptoms are very troublesome, estrogen replacement for 2 years may be the most direct and effective therapy. A high phytoestrogen diet is a health diet of soy and high quality vegetables. Coupled with regular exercise, these lifestyle recommendations may also have other benefits to the women. As for the herbs, they may fit the classic description of Voltaire, that the purpose of medicine is to amuse the patient while nature seeks a cure. ■

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# Another Tool for a Common Problem . . .

ABSTRACT & COMMENTARY

***Synopsis:*** *Intranasal fluticasone helps sleep-disordered breathing in patients with allergic rhinitis.*

**Source:** Kiely JL, et al. *Thorax*. 2004;59:50-55.

Kiely and colleagues studied a total of 23 patients with allergic rhinitis. There were 19 men and 4 women, and their mean age was 46 years. All of them were snorers. Using a definition for sleep apnea of an Apnea plus Hypopnea Index (AHI) >10 events/hr, 13 of these patients were classified with obstructive sleep apnea syndrome (OSAS). These 13 had a mean AHI of 30.3 and a mean lowest $Sa0_2$ 78%. 10 of these patients were classified as "nonapneic snorers" (mean AHI, 5; mean lowest $Sa0_2$, 86%). Patients were treated with in a randomized, double blind, placebo controlled design, with each treatment lasting 4 weeks. They all had polysomnography (with snoring measured by a nasion microphone), and nasal airflow resistance measured at enrollment, then at the end of each study period. They kept daily diaries of alertness, sleep quality, snoring intensity and nasal congestion throughout the study.

The apneics were sleepier (mean Epworth score, 12 vs < 9) and heavier (Body Mass Index, 29.8 vs 25.6 $Kg/m^2$) than the nonapneic snorers. The overall AHI was markedly reduced (from 20 to 11.9 event/hr) on fluticasone, compared with placebo, and for the apneic group it was 23.3 vs 30.3 on active drug vs placebo. Of note, the mean AHI was cut in half for the nonapneic snorers (from 5 to 2/7 events/h). Oxygen saturation was not sig-

nificantly different between phases of the study, nor was snoring intensity. Measures of objective sleep quality were generally no different between active drug and placebo, except for in increase in Slow Wave Sleep of borderline significance on placebo, but subjective alertness and symptoms of rhinitis were improved on fluticasone compared with placebo. Nasal airflow resistance was lower during active treatment. Kiely et al modestly conclude, ". . . the data indicate that intranasal corticosteroids are likely to have a limited clinical role in the management of OSAS, since most patients continued to have significant OSAS on treatment."

### COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Would that ENT surgeons were so modest!! Frankly, the results here are very similar to those reported by most studies of upper airway surgery as treatment for sleep apnea, except that Kiely et al actually measured and reported AHI and objective sleep structure on placebo and treatment, lost no one to follow-up, had a larger "n" than is typically reported in surgical studies, and didn't over state their findings.[1] If you haven't read the surgical literature lately, take a peek. Often, the "n" is 10-20 patients. Many are lost to follow-up. PSG data pre and post are rarely reported, and if they are, the patient is considered a "success" if the AHI is cut in half (which, as the authors of the current study point out, often leaves them with significant sleep-disordered breathing). Worse, instead of reporting PSG findings, surgical endpoints of "success" are often the Epworth Sleepiness Scale and some measures of snoring.

Yet patients with sleep-disordered breathing go to surgery every day. We encourage it, and their insurers pay for it. Why is this? Because CPAP, albeit very effective, is cumbersome, ongoing, unsexy treatment. Because surgeons tend to be very effective in marketing and in persuading insurers to pay. Because patients want a quick fix.

But it's important to know that there actually is a fair amount of literature suggesting that nasal steroids can be useful for patients with nasal rhinitis and sleep-disordered breathing.[2-5] And in the current study, Kiely et al used a fairly steep definition of sleep apnea; they required an AHI of 10 events or more to meet that definition. Many sleep clinicians and insurers in the United States define sleep apnea as an AHI of 5 events or more with symptoms. If we look at the group of non-apneic snorers reported here, it's interesting to note that their mean AHI fell from 5 to 2.7 events/hr on active treatment. Surgeons would call this a cure!!

Where does this leave us? I think it gives us one more tool in our armamentarium of treatment options for mild sleep-disordered breathing. Because of varying definitions of apneas, hypopneas, and sleep apnea itself, we still don't have a good handle on what the sequellae or prevalence of pathologic sleep-disordered breathing are. But we do know that those with milder disease tolerate CPAP less well, and we are often stuck, not knowing how best to help them. (*Of course* it would help if they lost weight—how often does that happen?). I personally have "cured" patients with mild sleep-disordered breathing and snoring with nasal steroids. And I think, in the long run, we are serving our patients better to write a prescription for a nasal steroid or to send them to the dentist than to send them to the surgeon if they can't or won't wear CPAP and have mild disease.


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# Rosuvastatin vs Atorvastatin

ABSTRACT & COMMENTARY


***Synopsis:*** *In heterozygous familial hypercholesterolemia patients, rosuvastatin produced significantly greater reductions in LDL cholesterol, increases in HDL cholesterol, beneficial changes in other lipid values, and achievement of NCEP cholesterol goals than observed with equivalent doses of atorvastatin, with a similar adverse event profile.*



**Source:** Stein EA, et al. *Am J Cardiol*. 2003;92: 1287-1293.


Rosuvastatin is a new statin whose efficacy was compared to that of atorvastatin in 623 patients with heterozygous familial hypercholesterolemia. The study design was 3:1 weight randomized to the new drug, double-blind, parallel group, and forced titration to 80 mg per day. There was a 6-week run-in period of no cholesterol-lowering drugs and the National Cholesterol Education Program (NCEP) step I diet. Then randomization was begun with 20 mg/d of each drug for 6 weeks, then 40 mg/d for 6 weeks, and finally 80 mg/d for 6 weeks. Subsequently, patients were offered an open-label, long-term extension on rosuvastatin 80 mg/d. The primary end point was

change in LDL cholesterol at 18 weeks. Mean LDL cholesterol after the 6-week run-in phase was 292 mg/dL in the rosuva group and 288 in the atorva group ($P$ = NS); HDL cholesterol was 48 and 47 and triglycerides were 160 and 159, respectively. Rosuva reduced LDL more than atorva (-58 vs -50%; $P < .001$) and increased HDL more (12 vs 3%, $P < .001$). Also, apolipoprotein B was reduced more and apolipoprotein A-1 was increased more by rosuva. Changes in triglycerides were similar with the 2 agents. The percentage of patients achieving NCEP LDL cholesterol goals was higher on rosuva (58 vs 44%; $P < .001$). Both agents reduced high sensitivity CRP similarly. Both drugs were well tolerated: adverse events resulting in drug discontinuation were 3% and 2%, with myalgia, asthenia, and nausea being most common. Clinically significant increases in alanine aminotransferase (> 3× upper limit of normal on 2 consecutive occasions) were observed in < 1% of patients. No clinically relevant increases in creatine kinase (> 10× upper limit of normal) occurred. Stein and associates concluded that in heterozygous familial hypercholesterolemia patients, rosuvastatin produced significantly greater reductions in LDL cholesterol, increases in HDL cholesterol, beneficial changes in other lipid values, and achievement of NCEP cholesterol goals than observed with equivalent doses of atorvastatin with a similar adverse event profile.

### COMMENT BY MICHAEL H. CRAWFORD, MD

For those patients who could not achieve cholesterol-lowering goals with 80 mg/d of atorvastatin, we used to have cervistatin until it was removed from the market due to excessive adverse events. Fortunately, we now have another potent statin alternative that seems to have a low incidence of adverse events. Even in the open-label extension, the incidence of clinically evident myopathy was < 1%. This is good news given the bad experience with cervistatin. What is also remarkable is the robust increase in HDL cholesterol with this drug (12%). Triglyceride values were also reduced but by a similar amount on both drugs. Whether these impressive changes in the lipid profile will translate to a reduction in clinical events that is greater with rosuvastatin remains to be proven. Interestingly, high-sensitivity CRP was reduced similarly by both agents.

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

# Coumadin and Mechanical Valves—What's the Right INR?

ABSTRACT & COMMENTARY

***Synopsis:*** *The meta-analysis by Vink and colleagues demonstrates that patients with either aortic or mitral valve replacement will benefit from high-intensity VKA therapy.*

**Source:** Vink R, et al. *JACC*. 2003;12:2042-2048.

Implanted mechanical heart valves have an increased risk of valve thrombosis often resulting in secondary systemic embolism both peripherally and into the cerebral circulation. Since life-long vitamin K antagonist (VKA) therapy (ie, usually Coumadin) significantly reduces the incidence rates of these serious complications, such therapy has been strongly recommended in the guidelines of the American College of Chest Physicians (ACP) since at least 1986.[1,2] However, since VKA therapy is, on occasion, associated with an increased incidence of severe and even fatal bleeding, the optimal intensity of VKA therapy has been defined as that intensity of therapy at which the incidence of both thromboembolic as well as bleeding complications is lowest. The 1986 ACP guidelines[2] recommended a prothrombin time with an international normalized ratio (INR) between 3.0 and 4.5 however, a significant study published in 1995 suggested that the optimal intensity of anticoagulation which resulted in the fewest adverse events was that intensity which resulted in an INR level between 2.5 and 4.9.[3] Finally, the 2001 ACP guidelines recommended an INR target range between 2.0 and 3.5 for patients with implanted mechanical heart valves. Vink performed a meta-analysis of all eligible studies published between 1965-2002 reporting data on the incidences of thromboembolic and bleeding complications occurring in patients with mechanical heart valves prostheses receiving different intensities of VKA therapy.[5] The 35 eligible studies reported findings in a total of 23,145 patients who were studied for 108,792 patient-years. The results revealed that patients with either aortic or mitral implanted mechanical valves would benefit when the target INR was higher than 3.0.

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

The intensity of anticoagulant therapy for patients with mechanical heart valves has long been the subject

of intense medical debate simply because adequate data has not been available. Because aortic valve prostheses have been considered less thrombogenic then prostheses in the mitral position,[4] the target INR at the upper end of the range of 2.0-3.5 has been suggested for mitral valve replacements whereas the lower end of the range has been advised for aortic valves.[5] The meta-analysis by Vink and his group demonstrates that patients with either aortic or mitral valve replacement will benefit from high-intensity VKA therapy since the number of thromboembolic events is lowest in both groups when the higher INR levels are targeted. Efficacy of treatment is clearly demonstrated because the total number of both thromboembolic and bleeding events in patients with aortic and mitral valve replacements were decreased in the high-intensity VKA therapy group..

The role of antiplatelet therapy in the long-term treatment of patients with mechanical heart valves remains controversial. One recent randomized trial[6] demonstrated that adding 100 mg/d of aspirin to VKA therapy (INR, 3.0-4.5) was associated with fewer thromboembolic events than VKA therapy alone, although the rate of major bleeding was increased. Results of another trial[7] revealed that aspirin (100 mg/d) in combination with VKA therapy was as effective as VKA therapy alone. These results do not provide sufficient evidence to recommend combination therapy however, until additional controlled studies are performed, the addition of antiplatelet therapy to VKA therapy should be considered for the prevention of thromboembolic events only in patients with exceptional thrombotic processes.

In conclusion, until a prospective study that addresses the intensity of VKA therapy in both aortic and mitral mechanical heart valve prostheses is performed, clinicians should consider increasing the target INR to between 3.0-4.5. and, since aortic prosthetic valves are considered less thrombogenic then prostheses in the mitral position, the target INR should be at the lower side of this range whereas the target INR should be in the upper side of this range for mitral prostheses. Obviously, a prospective controlled study is needed that will evaluate: 1) the benefits of varying intensities of VKA therapy in relationship to the position of the mechanical heart valve and, equally important, 2) whether or not antiplatelet therapy substantially diminishes the frequency of thromboembolism. ■

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## *Pharmacology Update*

# Olanzapine and Fluoxetine Capsules (Symbyax—Lilly)

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

THE FDA HAS APPROVED A COMBINATION OF OLANZAPINE and fluoxetine for the treatment of depressive episodes associated with bipolar disorder. Olanzapine is an atypical antipsychotic and fluoxetine is a selective serotonin reuptake inhibitor. The combination is marketed by Eli Lilly and Company as Symbyax.

### Indications

Olanzapine/fluoxetine is indicated for the treatment of depressive episodes associated with bipolar disorder.[1]

### Dosage

The recommended initial dose is olanzapine 6 mg/fluoxetine 25 mg once daily in the evening. The dose may be titrated to 12 mg of olanzapine and 50 mg of fluoxetine based on antidepressive effectiveness and tolerability.[1] Symbyax is available as 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg.

### Potential Advantages

Olanzapine/fluoxetine has been reported to be more effective than olanzapine alone in bipolar depression.[2] Olanzapine/fluoxetine may provide an effective and convenient treatment option for some patients with bipolar depression.

### Potential Disadvantages

The combination limits flexibility in optimizing drug combination selection and dosing. Most common adverse events are asthenia, somnolence, weight gain, dry mouth, and increased appetite. About 10% (vs 4.6% for placebo) of patients discontinued treatment in placebo-controlled clinical trials due to adverse events.[1]

### Comments

Olanzapine/fluoxetine is the first combination product to be approved for bipolar disorder. Its efficacy was sup-

ported by 2, 8-week, randomized, double-blind, controlled studies in patients with bipolar I disorder. Primary efficacy was assessed by the Montgomery-Asberg Depression Rating Scale (MADRS). This is a 10-item clinician rated scale ranging from 0 to 60. Secondary endpoints included treatment emergent mania and disease remission. Eligible patients had MADRS score of at least 20 and a history of at least 1 previous manic or mixed episode that required treatment with a mood stabilizer or an antipsychotic agent.[1,2] A total of 833 were randomized; 377 to placebo, 370 to olanzapine (5 mg initially and may be titrated to 20 mg/d), and 86 to olanzapine/fluoxetine (6 mg/25/d initially and may be titrated to 12 mg/50 mg). The percent of responders (≥ 50% improvement in MADRS) were 56.1% for olanzapine/fluoxetine, 39% for olanzapine, and 30.4% for placebo. Median time to response was 21 days, 55 days, and 59 days for olanzapine/fluoxetine, olanzapine, and placebo respectively. Remission rates were 48.8%, 32.8%, and 24.5% respectively. Olanzapine/fluoxetine was statistically different than olanzapine and placebo in all the above end points. No significant difference was observed in treatment-emergent mania among the three groups. Most common side effects were somnolence (21%), weight gain (17%), dry mouth (16%), increased appetite (13%), and asthenia (13%).[2] No comparisons between olanzapine/fluoxetine and lithium or other drugs or drug combinations have been published. The wholesale cost of olanzapine/fluoxetine is about $6.50 per day for 6 mg of olanzapine and about $10 per day for 12 mg of olanzapine.

### Clinical Implications

Bipolar disorders have a lifetime prevalence of 1.6-1.8%.[3] Bipolar I depression is characterized by episodes of mania and depression while bipolar II is characterized by hypomania and depression. Treatment involves managing acute manic and depressive episodes and stabilizing mood fluctuation. This may require various combinations of mood stabilizers and antidepressants.[4] For acute depression in bipolar patients not yet in treatment for bipolar disorder, the American Psychiatric Association (APA) recommends initiating with lithium or lamotrigine. An alternative is lithium with an antidepressant. For patients with breakthrough depressive episodes APA recommends adding lamotrigine, bupropion, or paroxetine.[5] Other treatments have included anticonvulsants (eg, valproate, carbamazepine) atypical antipsychotics (eg, olanzapine, risperidone).[5] Olanzapine is currently FDA approved for acute mixed or manic episodes associated bipolar I disorder and may be appropriate as monotherapy for less ill patients.[5] The combination of olanzapine and fluoxetine has been shown to be more effective in bipolar I depression than olanzapine alone. The use of this combination is, however, limited by its lack of flexibility and clinical experience. ■

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## CME Questions

5. **Anticoagulant therapy for patients with mechanical heart valves:**
   a. should be targeted to produce an INR in the range of 3.0-4.5.
   b. may be combined with antiplatelet therapy in selected patients.
   c. should be of sufficient intensity to produce an INR at the upper end of the range in patients with a mechanical mitral prosthesis.
   d. All of the above

6. **Which of the following is true regarding the use of nasal steroids to treat sleep apnea?**
   a. Subjective alertness improves.
   b. Snoring is eliminated.
   c. Oxygen saturation improves.
   d. The AHI changes only minimally.
   e. This is standard treatment for sleep apnea.

7. **Evidence supports the use of the following interventions for hot flashes except:**
   a. Evening Primose
   b. Black Cohosh
   c. Phytoestrogens
   d. Exercise
   e. Progesterones

**Answers:** 5 (d); 6 (a); 7 (a)

## Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Internal Medicine Alert*. Send your questions to: Robert Kimball, *Internal Medicine Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Internal Medicine Alert* via the internet by sending e-mail to robert.kimball@ahcpub.com. We look forward to hearing from you ■

*By Louis Kuritzky, MD*

## Efficacy and Safety of Low-Dose Aspirin in Polycythemia Vera

THE INCREASED RED CELL MASS diagnostic of polycythemia vera (PCV) results in blood hyperviscosity, which is associated with increased thrombotic events. Initial enthusiasm for the concept of ASA thromboprophylaxis in PCV was dampened by a 1986 trial of aspirin (ASA) at a dose of 900 mg/d, in which an unacceptably high incidence of major GI bleeding was seen. In non-PCV populations, low-dose ASA has been shown to provide effective thromboprophylaxis, with lesser risk of major GI bleeding.

Plasma thromboxane (a direct stimulator of platelet activation) levels are elevated as much as 10 fold in PCV, a situation parallel to that seen in acute coronary syndromes, in which ASA has been proven to provide dramatic risk reduction. Since even low-dose ASA results in substantially reduced platelet thromboxane production, but less GI bleeding, the potential merit of such a clinical trial is straightforward.

PCV patients lacking any other direct indication for ASA (eg, previous MI) were enrolled in a double-blind placebo-controlled randomized trial to compare 100 mg ASA with placebo (n = 518). The 2 primary end points of the study were: 1) nonfatal MI + nonfatal stroke + CV death; 2) nonfatal MI + nonfatal stroke + PE + DVT + CV death. Secondary end points included individual thrombotic components of the above.

After a mean followup of 3 years, ASA reduced the primary end point #2 by 60%; primary end point #1 was reduced 59%, but did not achieve statistical significance. The lower ASA dose (100 mg/d) demonstrated excellent safety, with no statistically significant increased risk of either major or minor bleeding compared to placebo. Landolfi and associates recommend consideration of low-dose ASA for thromboprophylaxis in PCV. ■

*Landolfi R, et al. N Engl J Med. 2004; 350:114-124.*

## Coronary Artery Calcium Score Plus Framingham Score for Risk Prediction

THE FRAMINGHAM RISK SCORE (FRS) is a commonly recommended tool for estimating risk of coronary events (CHD) in asymptomatic persons (asymptomatic for CHD, that is). It provides an assessment of the likelihood of experiencing a CHD event in the next 10 years. Despite inclusion of age, sex, smoking, BP, lipids, and glucose, the FRS is imperfect in identifying those at CV risk, especially for those determined to be at 'intermediate risk' (FRS = 10-19%). Another tool used for CHD risk stratification is coronary artery calcium scoring (CACS), as obtained by CT. The purpose of this trial was to ascertain whether combining the 2 enhances accuracy.

Asymptomatic persons older than 45 (n = 1461) with at least one CHD risk factor (but without prior MI or proven CAD) were enrolled. Diabetics were excluded because CACS has not proven effective in this population, who are by definition already recognized as high risk for CAD at presentation. Patients were followed up to 8.5 years (mean, 7 years).

For persons with a FRS of at least 10% (but < 20%), a CACS greater than 300 (highest quartile CHD risk) significantly modified risk prediction. For instance, a FRS 10-year risk prediction of 10% was increased to 13-19% when coupled with a CACS score > 300. Greenland and associates suggest that for low-risk (FRS < 10%) and high risk (FRS > 20%) individuals, CACS adds little. Prognostication about the intermediate risk group (FRS = 10-19%) is enhanced by combining the tools. ■

*Greenland et al. JAMA. 2004;291: 210-215.*

## Intra-Articular Hyaluronic Acid in the Treatment of Knee Osteoarthritis

THE USE OF HYALURONIC ACID (HUA) injection in human subjects began in 1997, following a history of similar treatment in veterinary medicine. HUA is a constituent of normal synovial fluid, and has been conceptualized as a 'joint lubricant.' Because of mixed efficacy responses in clinical trials, clinician acceptance of this treatment modality for osteoarthritis of the knee (OA) has been somewhat tepid.

This metaanalysis included 22 trials, with almost 3000 patients. To quantify treatment effects, an 'effect size' metric was used; 0.2-0.5 is a 'small' effect size, comparable to the advantage of NSAIDs over acetaminophen in OA treatment trials. Analysis included all recipients of HUA injection, but was further separated out into groups based upon whether subjects had received standard, or highest molecular weight HUA.

Overall, HUA was found to provide a modest benefit (effect size = 0.32); Lo and associates discuss that even this result may be overoptimistic, since publication bias was discerned amongst HUA injection trials. According to this analysis, whether highest molecular weight HUA is more advantageous than other configurations remains indeterminate. Lo et al call for further independent trials to provide greater clarifiation of HUA efficacy. ■

*Lo GH, et al. JAMA. 2003;290: 3115-3121.*

# What a Difference a Lead Makes

*By Ken Grauer, MD*

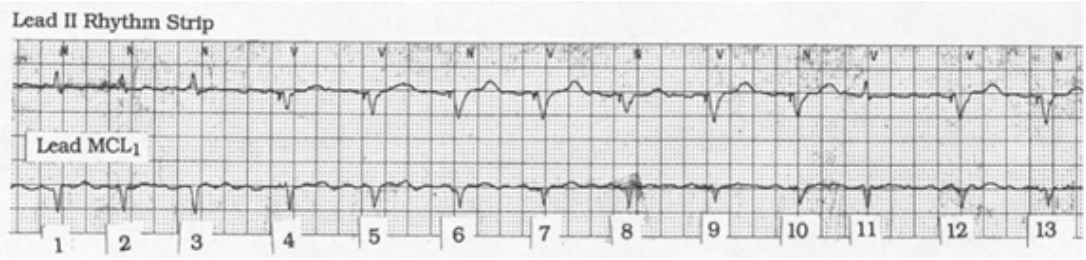


**Figure.** Telemetry rhythm strip obtained from a 67-year-old woman with heart failure

**Clinical Scenario:** The telemetry rhythm strip shown in the Figure was obtained from a 67 year old woman who presented with heart failure. A permanent pacemaker had been implanted a number of years earlier. Interpret the tracing initially by looking *only* at lead $MCL_1$. How does the addition of a second simultaneously recorded lead (lead II) help in your interpretation? How many findings can you identify on this two-lead telemetry tracing? (Hint: Some of these findings are very subtle!)

**Interpretation/Answer:** Accurate interpretation of this tracing would be virtually impossible if one only had access to a single MCL1 monitoring lead. This is because the QRS complex looks similar for virtually all beats in MCL1, and pacer spikes are practically nondetectable in this lead. This highlights the importance of viewing arrhythmias from more than the limited perspective of a single monitoring lead. Addition of lead II to our database allows identification of regular ventricular pacing spikes at a rate of 80/minute for much of the tracing (beats #4 through 10 and 12-13 are paced). Each pacer spike is followed by a QRS complex and T wave, indicating appropriate capture. Several spontaneous beats are seen on the tracing (beats #1, 2, 3 and 11). From the complete absence of P waves, the presence of fine undulations in the ECG baseline, and apparent irregularity of spontaneous beats #1, 2, and 3, the underlying rhythm appears to be atrial fibrillation. Appropriate sensing of the pacemaker is suggested by the absence of pacer spikes during the spontaneous rhythm, with appropriate return of pacer spikes following the two brief pauses that occur after beat #3 and beat #11. Note that the R-R interval preceding the pacer spikes occurring after these two pauses (ie, the R-R interval between beats #3-4 and 11-12) is virtually the same as the R-R interval during the 7-beat sequence of consecutively paced beats (that occurs between beats # 4-10). This confirms that the pacemaker is appropriately sensing as well as capturing the ventricles.

The final finding of interest relates to the presence of fusion beats. The importance of recognizing this finding on a pacemaker tracing is primarily so that one does not misinterpret the changes in QRS morphology that may result as indicative of ventricular ectopy or pacer malfunction. Fusion beats are commonly seen in patients with pacemakers (especially when the underlying spontaneous rhythm is atrial fibrillation), since the presence of the pacemaker itself predisposes to a situation in which some spontaneous beats are likely to occur (by chance alone) in close temporal proximity to paced impulses. The result of near simultaneous occurrence of a spontaneously occurring supraventricular impulse (from the patient's atrial fibrillation) with an impulse originating for the ventricles (from a paced beat) is a "fusion" complex that manifests characteristics of *both* the spontaneous beat and the paced QRS complex. Thus, the paced QRS complexes of both #4 and 5 are clearly not as wide in lead II as the other paced beats—a result of *fusing* QRS morphology of spontaneous beats with completely paced complexes. Note that the T wave in lead II of these fusion beats (ie, the T wave of beats #4 and 5) is not as prominent as the T wave of fully paced beats #6, 7, 9, 10, 11, and 12. In addition to a fusion effect on QRS morphology, near simultaneous occurrence of a supraventricular beat and a paced ventricular complex may also produce a fusion effect on T wave appearance. Awareness of this last point supports our suspicion that the slight alteration in QRS and T wave morphology of paced beat #8 also reflects some degree of fusion between this paced beat and a spontaneously occurring impulse from this patient's underlying atrial fibrillation. ■

**In Future Issues:** Coronary Angioplasty vs Standard Therapy

# PHARMACOLOGY WATCH

## Valacyclovir Reduces Genital Herpes Transmission

A once-a-day dose of a valacyclovir reduces the rate of transmission of genital herpes (HSV-2) from an infected partner to an uninfected susceptible partner, according to a new study. The study group included 1484 immunocompetent, heterosexual, monogamous couples in which 1 partner had symptomatic genital HSV-2 and the other was susceptible to HSV-2. The infected partners were randomized to valacyclovir 500 mg once daily or placebo for 8 months. At the end of the study period, clinically symptomatic HSV-2 infections developed in 4 of 743 susceptible partners in the valacyclovir group vs 16 of 741 in the placebo group (HR, 0.25; 95% CI, 0.08-0.75; $P = 0.008$). Overall acquisition of HSV-2, including asymptomatic infections, was observed in 14 partners in the valacyclovir group compared to 27 in the placebo group (HR, 0.52; 95% CI, 0.27-0.99; $P = 0.04$). Valacyclovir significantly cut down on viral shedding in the infected partner and also significantly cut down on the rate of HSV-2 outbreaks in the infected partner. The authors caution that 37% of couples in the study did not use condoms even though counseled to do so, and that condom use and abstinence during attacks are the most effective methods of preventing transmission (*N Engl J Med*. 2004;350:11-20).

### *Erythropoietin Safe for Cancer Patients?*

A fascinating news item published in the December 17 issue of *Journal of the National Cancer Institute* raises the question of whether erythropoietin is safe to use in cancer patients. According to the news report, several studies suggest that many cancer cells have erythropoietin receptors that may be stimulated by erythropoietin injections. Erythropoietin is commonly given to cancer patients to treat chemotherapy-related, or cancer-related anemia. Two recent trials have shown that erythropoietin use is associated with decreased survival in some cancer patients according to the news report. Erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. Preliminary data suggest that some of these cancers may actually proliferate in the presence of erythropoietin. The association between erythropoietin and decreased survival for some cancer patients needs further evaluation (*J Natl Cancer Inst*. 2003;95:1820-1821).

### *WHI, ALLHAT Trials Still Spur Research*

It appears that 2 landmark studies have significantly changed practice patterns in this country. The Women's Health Initiative (WHI) study published in July 2002, and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) published in April 2000 both showed negative results with some of the most widely prescribed pharmaceuticals in this country. WHI suggested that combined estrogen/progesterone increases the risk of breast cancer and cardiovascular disease in postmenopausal women. Researchers from Stanford looked at prescription trends in hormone therapy from 1995 to July 2003. Annual hor-

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mone therapy prescriptions increased dramatically between 1995 in 1999 and then remained stable through June 2002. Following publication of the WHI in July 2002, prescriptions for Prempro, the combination estrogen/progesterone used in the study, declined by 56%. New prescriptions for conjugated estrogen also declined significantly. Small increases were seen with topical estrogens and low-dose estrogen preparations over the same time period (*JAMA*. 2004;291:47-53). ALLHAT was terminated early and the results released in December 1999, and published in April 2000 because early results showed that doxazosin, an alpha-blocker, was significantly inferior to diuretics with respect to preventing stroke, congestive heart failure, and a composite of other cardiovascular outcomes. The same group from Stanford reviewed alpha-blocker prescription trends from 1996 to 2002. Steady increases in alpha-blocker prescriptions were seen in between 1996 and 1999, but new prescriptions for the drugs declined 26% between 1999 and 2002. Changes in pricing, generic version, drug promotion, or competition did not have a confounding effect. The authors conclude that modest declines in alpha-blocker prescribing were seen after publication of ALLHAT (*JAMA*. 2004;291:54-62).

### Alpha-Blockers Useful in BPH Treatment

Alpha-blockers are useful in treatment with benign prostatic hyperplasia (BPH). Now a new study shows that the combination of the 5-alpha-reductase inhibitor finasteride (Proscar) with an alpha-blocker may be superior to either drug alone in treating BPH. Researchers randomized 3047 men to placebo, doxazosin, finasteride, or combination therapy with the end point of clinical progression of BPH. Clinical progression was defined as an increase in the American Urologic Association symptom score of these 4 points, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection. Both doxazosin and finasteride significantly reduced clinical progression (doxazosin-39% risk reduction, $P < 0.001$; finasteride 34% risk reduction $P = 0.002$) compared to placebo. The combination of doxazosin and finasteride however resulted in a 66% risk reduction compared with placebo ($P < 0.001$). Mean follow-up was 4.5 years. The authors conclude that long-term combination therapy with doxazosin and finasteride was safe and significantly reduced the risk of clinical progression of BPH and was superior to either drug alone (*N Engl J Med*. 2003;349:2387-2398).

### T4 Alone is OK for Hyperthyroidism Therapy

Hypothyroidism is one of the most common clinical disorders in general practice. Controversy about replacement therapy has raged for years regarding the need for liothyronine (T3) in addition to thyroxine (T4). A new study from Bethesda suggests that thyroxine alone is optimal therapy. In this randomized, double-blind, placebo-controlled trial, 46 hypothyroid patients were randomized to their usual dose of levothyroxine, or combination therapy in which their dose of levothyroxine was decreased by 50 µg/d, and liothyronine 7.5 µg was given twice daily for 4 months. TSH levels were followed and remained stable throughout the study. The main outcomes were scores on the hypothyroid specific health-related quality of life questionnaire, body weight, serum lipid levels, and 13 neuropsychological tests before and after treatment. After 4 months, body weight and serum lipid levels were unchanged in both groups. Quality of life scores improved in both groups (23% improvement levothyroxine group [$P < .001$], 12% improvement combination group [$P = .02$]). There is no statistical difference in neuropsychological testing between the 2 groups except for better performance in the Grooved Peg Board test in the levothyroxine group. The authors conclude combination therapy with levothyroxine plus liothyronine offers no advantage over single therapy with levothyroxine for the treatment of hypothyroidism (*JAMA*. 2003;290:2952-2958).

### FDA Ban on Ephedra Awaits Final Ruling

The FDA has issued a consumer alert, banning the dietary supplement ephedra. The ban will become effective 60 days after the publication of a final rule stating that dietary supplements containing ephedra represents an unreasonable risk of illness or injury. This unprecedented move, the first time the FDA has banned a supplement, comes after several high-profile deaths linked with ephedra including professional athletes. Overall, the FDA has reports of 155 deaths associated with ephedra and more than 16,000 complaints. The drug is commonly used for weight loss and is present in many over-the-counter preparations. It is also widely used in Chinese herbal medicine practices, where it is known as Ma huang, and has been a staple of therapy for thousands of years for a variety of ailments including asthma and fever. The FDA has allowed an exemption for practitioners of Chinese medicine as long as is not used in high dose for weight loss. ■