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INSIDE

Keeping Abreast

ABSTRACT & COMMENTARY

Synopsis: *Exercise reduces the risk of breast cancer after menopause. Although the exercise need not be strenuous, longer duration of exercise confers greater benefit.*

Source: McTiernan A, et al. *JAMA*. 2003;290:1331-1336.

This study was part of the Women's Health Initiative (WHI). A total of 93,676 women aged 50-79 were enrolled between October 1993 and December 1998. Those with serious underlying illness, known breast cancer, or missing data were excluded. Women were recruited from 40 different centers, and about 15% were of color. They were followed by medical questionnaires annually, with about 95% response rates for each of the 6 subsequent years. Historical exercise was ascertained by asking (yes or no) if they did exercise that was long enough to work up a sweat and make their heart beat fast at least 3 times a week when they were 18, 35, 50, and current age at study entry. Current exercise was further assessed by asking how often they did the aforementioned exercise at study enrollment, as well as how often they currently walked outside the home for more than 10 minutes without stopping; they could choose between rarely/never, 1-3 times per month, weekly, 2-3 times per week, 4-6 times per week, and 7 or more times per week. Information about speed and duration was also gathered. They were also queried about moderate- and low-intensity exercise, with examples provided. Using midpoint values for ranges of frequency and duration of exercise reported, McTiernan and colleagues assigned metabolic equivalent (MET) values to the reported weekly activity and calculated MET~hours/week. Reproducibility and validation of this system was tested on a subset of more than 500 participants; test-rest reliability was very good. Detailed information about behavioral risks, age at menopause, menstrual and reproductive history, family risk factors, hormone replacement therapy, and diet was also collected. The women were followed up a mean of 4.7 years later, and there were 1780 newly diagnosed cases of breast cancer.

Past exercise: Women who engaged in strenuous physical activity at least 3 times a week at ages 35 and 50 had a reduction in over-

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all breast cancer risk that was statistically significant only for the "exercise at 35" bracket. However, invasive cancer risk was markedly reduced for those who exercised at either 35 or 50. Exercise at 18 did not appear to confer much benefit.

Current exercise: There was an inverse "dose response" relationship between exercise at enrollment and breast cancer risk: those expending > 5-10 MET/week had an 18% reduction in breast cancer compared with sedentary women, and those expending > 40 MET/week had a 22% reduction. Similarly, more than 7 hours/week of strenuous exercise was associated with a 21% reduction in risk of breast cancer. These relationships held except for the most obese, even when controlling for Body Mass Index (BMI), the most obvious covariate. They also held when controlling for waist circumference, and behavioral and biologic risk factors.

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COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

This is the largest, most carefully done study of the relationship between exercise and breast cancer to date. Previous studies have shown that exercise is associated with a reduced risk of breast cancer,[1-4] but the current study is larger, makes an attempt to quantify exercise, and controls for most known important variables.

You know who needs to hear this? Your "worried well" women, who don't smoke, take vitamins, and worry about their health. Exercise is a potent defense against most of the ills associated with aging, including cancer, diabetes, obesity, and arthritis. And the odds are that your female patients will need this message more than your male patients. Data from the 2000 National Health Interview Survey indicate that fewer women than men exercise regularly.[5]

The editorial accompanying this article[6] attempts to reconcile (and apologize) for 2 conflicting reports on the need for exercise: that from the Centers for Disease Control (CDC)[7] and that from the Institute of Medicine (IOM).[8] The CDC recommends 30 minutes a day of moderate physical activity. The IOM is more focused on weight control and recommends 60 minutes a day of moderate-intensity exercise. This reminds me a little bit of the prune commercial, ". . . a half a dozen too many? Six not enough?" Any exercise at all would be a big step for most Americans; in fact, 72% of women and 65% of men do not engage in regular leisure time physical activity.[5] The people writing these reports have not been to a mall or taken public transportation lately. A minority of people in America exercise. Our job is to get our patients moving! Any exercise at all is more than most are getting. ■

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System Breakdown

ABSTRACT & COMMENTARY

Synopsis: *Most postmenopausal women who suffer a fracture do not receive treatment for osteoporosis.*

Source: Andrade SE, et al. *Arch Intern Med*. 2003;163: 2052-2057.

Osteoporotic fractures are an important contributor to morbidity and mortality.[1,2] Patients with hip fractures run a 10% risk of disability and 19% require institutionalization. They account for 140,000 nursing home admissions annually. Fractures can be a source of chronic pain. They interfere with the activities of daily living and have a negative effect on quality of life. The US price tag for osteoporotic fractures is estimated to be $17.5 million annually. Among postmenopausal women, 90% of fractures are associated with osteoporosis.[3] Compared to a person who has neither osteoporosis nor a history of fracture, a person with both has an increased risk of sustaining another. There exist several medications (alendronate [Fosamax®], calcitonin [Miacalcin®], calcium, estrogens, raloxifine [Evista®], risendronate [Actonel®], and teriparatide [Forteo®]) approved by the Food and Drug Administration for the prevention of osteoporosis. Treatment with these drugs usually results in an increase in bone mineral density and reduced risk of fracture within a year or two. It stands to reason, then, that physicians should treat postmenopausal women who suffer fractures for osteoporosis. Is this reality?

Andrade and colleagues address that question by mining the databanks of 7 geographically diverse health maintenance organizations (HMOs). Looking at data from 1994 to 1996, they identified 3492 women, at least 60 years old, who suffered a wrist, vertebral, or hip fracture. They excluded those who had concurrent cancer diagnoses (to exclude pathologic fractures), multiple myeloma, and major trauma.

The primary outcome was a dispensing of a drug (estrogen, bisphosphonate, or calcitonin) that treats osteoporosis. The breakdown (pardon the pun) was 1572 (45%) hip fractures, 1620 (46%) wrist fractures, and 300 (9%) vertebral fractures. In the 90-day period before their fractures, 2995 of these women were enrolled in their HMOs. Of these, only 390 (13%) were receiving a drug indicated for osteoporosis. In the year after their fractures, 822 of 3492 (24%) were receiving such a drug. When examining rates by fracture site, women with vertebral fractures were more likely (44%) to receive an osteoporosis drug than women with wrist (23%) or hip fractures (21%). The older a woman was, the less likely she was to receive medications, 33% for ages 65-70 years old vs 15% for those 80 or older. There was an increase in dispensing when comparing rates for 1994 (22%) and 1996 (26%). There were 2605 women who were not receiving an osteoporosis drug before their fracture; only 353 (14%) were receiving one in the year afterward. Of the 390 women who were receiving a drug before their fracture, 365 were in the following year.

COMMENT BY ALLAN J. WILKE, MD

Not much to cheer about here. As primary care physicians, our goal is primary prevention; secondary prevention is second best. This study indicates that for postmenopausal osteoporosis we are not addressing either effort. We have not corralled the horse, let alone closed the barn door before it got out. What I find very troubling is that this population was drawn from HMOs who had prescription drug benefits and who, presumably, had greater access to health care and screening for osteoporosis. What would the results have been if the population had been our run-of-the-mill Medicare patients? Another consideration is that it is likely that the women receiving estrogen in the 90-day period before a fracture (353 of 2995) were not receiving it exclusively for bone health. And this was during the time before the Women's Health Initiative (WHI), when many of us were enthusiastically endorsing the use of estrogen for better bones! (By the way, the WHI demonstrated that estrogen plus progesterone did increase bone mineral density and reduced the risk of fracture in their study group.[4] The researchers decided that the absolute risk reduction, 2.5%, was insufficiently robust to outweigh the adverse effects of hormone replacement therapy, even in the group of women at high risk for fracture.)

Andrade et al speculate why undertreatment was so prevalent and came up with several plausible causes. They included "clinical inertia" and physician skepticism regarding the evaluation of osteoporosis and the efficacy of treatment. However, the reasoning that I find most compelling is health care system dysfunction and the breakdown of communication between the physician who treats the fracture and the physician who provides continuity of care. Simonelli queried orthopedic surgeons and primary care physicians about who was responsible for what in the care of patients hospitalized with a fragility fracture.[5] The orthopedic surgeons were in agreement that the primary care physician owned the responsibility for postfracture treatment of osteoporosis. This kind of specialty territoriality can only contribute to patients falling through the cracks and sustaining another fracture (again, pardon me).

Are there any reasons to doubt the findings of this study? It was conducted retrospectively and examined databases from 1994 to 1996. Could we be doing a better job in 2003? Not likely. Feldstein looked at her HMO population over the years 1998 and 1999.[6] Of the 2804 men and women, aged 50 to 89 years, who sustained a fracture, only 34.7% were on an osteoporosis medication and only 4.6% had new use after the incident fracture. When looking at women alone, the rate of treatment was better (42.4%) but still suboptimal. More than 90% of this population had a prepaid drug benefit.

There are several clinical guidelines that recommend routine screening and treatment of asymptomatic osteoporosis in postmenopausal females.[7-10] The bottom line is that we must increase our efforts to identify patients at risk for osteoporosis and prescribe treatment. This is a situation where an electronic medical record could be enormously valuable: "Computer, please prepare me a list of all my patients who are 65 years or older and who have not had a DEXA scan." If only practice were this easy. ■

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Treatment of CAP with Levofloxacin

ABSTRACT & COMMENTARY

Synopsis: *Treatment of CAP with 750 mg of levofloxacin daily for 5 days was as effective as a 10-day course of 500 mg daily.*

Source: Dunbar LM, et al. *Clin Infect Dis*. 2003;37:752-760.

Dunbar and colleagues at 70 US sites randomized, after stratification by severity, 530 adults with community-acquired pneumonia (CAP) to receive 1 of 2 regimens of levofloxacin—750 mg daily for 5 days or 500 mg daily for 10 days. A total of 122 patients had relatively mild disease, with pneumonia severity index (PSI) scores ≤ 70. All but 3 of the remaining patients had PSI scores of 71-130. The most frequently encountered among the 158 infectious etiologies identified was *Mycoplasma pneumoniae*, which accounted for 79 (50%), followed by *Streptococcus pneumoniae* (27%) and *Chlamydia pneumoniae* (24%). There were 11 *Legionella pneumophila* infections in the 5-day group and only 3 in the 10-day group.

The clinical success rates among the 390 evaluable patients were similar in the 2 treatment groups at 92.4% and 91.1%, respectively. Defervescence occurred significantly more rapidly in the 750 mg group. The frequency of subsequent clinical relapse did not differ significantly between those receiving 5 days of treatment (4.3%) and 10 days (1.2%). Microbiological efficacy also did not differ between the 2 treatment arms and was ≥ 90% in each arm for each identified pathogen. Seven cases of pneumococcal bacteremia were detected in each arm, with all but (possibly) 1 being cured.

There were no signicant differences in the frequencies of drug related adverse events.

■ COMMENT BY STAN DERESINSKI, MD, FACP

This study demonstrates that a 5-day course of 750 mg levofloxacin daily is not inferior to a 10-day course of 500 mg daily. The rationale for the shorter course with a higher dose has sound bases. The antibacterial activity of fluoroquinolones is concentration-dependent, and outcome of infection appears to be most closely linked to the achieved C_{max}/MIC and AUC/MIC, both of which are optimized at higher doses. In addition, the blood levels achieved with the 500 mg daily dose of levofloxacin may be becoming marginally effective in some areas as the MIC of *S pneumoniae* creeps upward. Such marginally effective concentrations may also increase the likelihood of selection of resistant mutants. A CDC study has demonstrated a reduced risk of selection of resistant pneumococci in nasopharyngeal cultures of children given higher-dose, shorter-course amoxicillin than the reverse.[1] This analogy is not perfect, however, since beta-lactams exhibit time-dependent, rather than concentration-dependent, activity. Also, however, in terms of gross tonnage, the shorter course levofloxacin regimen exposes the bacterial ecology to a total of 25% less antibiotic.

Some caveats are warranted. It is reported that 140 of the 530 (26%) randomized patients were not clinically evaluable. With the exception of 3 patients, those with

the most severe pneumonia (PSI >130) were not included in this study. In addition, an etiologic agent was apparently identified in only a minority of cases and one-half of these were believed to be due to *M pneumoniae*. The identification of this etiology, as well as *C pneumoniae*, relied on serological testing. However, Dunbar et al neglect to indicate the methodology, whether a central laboratory was used, and what the criteria for diagnosis were. Thus, one could question these diagnoses.

The 750 mg dose appeared to be well tolerated. This is not surprising since this dose has received US FDA approval in both skin/skin structure infection and nosocomial pneumonia. ■

Reference

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Dr. Deresinski is Clinical Professor of Medicine, Stanford; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, Santa Clara, Calif.

Pharmacology Update

Memantine Hydrochloride Tablets (Namenda)

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

THE FDA HAS APPROVED THE FIRST DRUG FOR THE treatment of moderate-to-severe Alzheimer's disease (AD). Memantine, a noncompetitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor, has been available outside of the United States since 1982. It is licensed from Merz Pharmaceuticals in Germany and is marketed by Forest Pharmaceuticals as Namenda.

Indications

Memantine is indicated for the treatment of moderate-to-severe dementia of the Alzheimer's type.[1]

Dosage

The starting dose is 5 mg once daily with a target dose of 20 mg daily. The dose should be increased in 5-mg increments at one-week intervals as follows; 5 mg twice daily, 5 mg and 10 mg as separate doses, and 10 mg twice daily.[1] The drug may be taken without regard to meals. Dose reduction show is considered in patients with moderate renal impairment.[1]

Memantine is available as 5-mg and 10-mg tablets.

Potential Advantages

Memantine is the first drug approved for the treatment of moderate-to-severe AD. Results from clinical trials indicated that patients randomized to memantine or memantine plus donepezil were more likely to show a slower deterioration of disease compared to placebo or donepezil plus placebo.[1-4] Less caregiver time was needed for patients who received memantine compared to placebo.[2,5] Memantine is well tolerated and is not likely to interact with drugs metabolized by the cytochrome P450 isoenzymes.[1]

Potential Disadvantages

The most common side effects associated with memantine were dizziness (7% vs 5% for placebo), headache (6% vs 3%), and confusion (6% vs 5%). Twenty three percent of patients discontinued memantine in the clinical trial that compared memantine with placebo.[2] Memantine may interact with other NMDA inhibitors such as amantadine, ketamine, and dextromethorphan, and food or drugs that increase of pH of the urine may lead to accumulation of the drug in the body. There is currently no evidence that the drug affects the underlying neurodegeneration of AD.[1]

Comments

Memantine is the first noncholinesterase inhibitor approved for the treatment of AD. In contrast, memantine acts on the glutamatergic system, as stimulation of the NMDA receptor by glutamate has been speculated to have a role in the disease.[6] Memantine showed a better outcome than placebo as assessed by Alzheimer's Disease Cooperative Study Activity of Daily Living inventory (ADCS-ADL) (0-54 scale) and the Severe Impairment Battery (SIB). ADCS-ADL measured 19 items of functional capacity such as ability to eat, dress, bathe, telephone, shop, travel, and performing household chores. SIB (0-100 scale) measured 9 areas of cognitive performance including attention, orientation, language, memory, visuospatial ability, construction praxis, and social interaction. These patients all had difficulties with self-care functions such as dressing, bathing, and toilet use at baseline. In a 28-week study (n = 252), a mean difference of 3.4 units in ADCS-ADL and 5.7 units in SIB was seen with memantine compared to placebo.[1,2] Similarly, in a 24-week study (n = 404), patients on memantine plus donepezil showed a difference of 1.6 units in ADCS-ADL and 3.3 units in SIB compared to donepezil and placebo.[1] Analyses were based on intent to treat and last observation carried forward. A difference in caregiver

time of about 50 hours per month was reported for the memantine group.[2,5] A favorable trend in favor of memantine was reported in the time to institutionalization.[5] While memantine showed measurable differences in some quantitative scales, there is no evidence that memantine slows the underlying neurodegeneration of the disease.[1] No significant difference was seen with the Mini-Mental State Examination score, Global Deterioration Scale stage, or Neuropsychiatric Inventory score.[2] These measure cognitive function, overall cognitive and functional capacity, and neuropsychiatric disturbance respectively. Memantine appears to be well tolerated, and the frequency of side effects was not significantly different than placebo.[1] Significant cognitive benefit also been reported in patients with mild-to-moderate vascular dementia, but the global Clinician's Interview Based Impression of Change (CIBIC-plus) did not reach statistical significance.[7] Memantine is expected to be available in January 2004. The wholesale cost of memantine was not available at the time of this review.

Clinical Implications

AD is believed to affect about 4.5 million Americans, increasing as the population ages. Currently, 4 cholinesterase inhibitors (tacrine, donepezil, galantamine, and rivastigmine) are available for the treatment of mild-to-moderate disease. Memantine is the only drug approved for moderate-to-severe disease and has shown measurable difference in certain quantitative measures of disease symptoms at 24-28 weeks. The effect of the drugs has been characterized by the FDA's Peripheral & Central Nervous System Drugs Advisory Committee as "small but consistent."[8] The role of memantine in less-severe disease and the role of a combination with a cholinesterase inhibitor remains to be determined by clinical trials. ■

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CME Questions

22. With regard to the relationship between exercise and breast cancer risk:

a. postmenopausal exercise reduces the risk of breast cancer, but premenopausal exercise does not.
b. postmenopausal exercise does not reduce the risk of breast cancer, but premenopausal exercise does.
c. both postmenopausal and premenopausal exercise reduces the risk of breast cancer.
d. neither postmenopausal exercise nor premenopausal exercise reduces the risk of breast cancer.
e. exercise does not appear to be related to the risk of breast cancer.

23. Choose the one correct statement.

a. The majority of postmenopausal women who suffer an osteoporotic fracture are prescribed a drug to increase bone mineral density.
b. The older the woman, the less likely she is to receive anti-osteoporosis medication.
c. Women with hip fractures are more likely to receive anti-osteoporosis medication than women with wrist fractures.
d. Among postmenopausal women, 50% of fractures are associated with osteoporosis.
e. Hip fractures were less common than vertebral fractures among postmenopausal women.

Answers: 22 (c); 23 (b)

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We look forward to hearing from you. ■

By Louis Kuritzky, MD

Parathyroid Hormone and Alendronate Alone or in Combination in Postmenopausal Osteoporosis

The prevention and treatment of osteoporosis (OSPS) present formidable public health issues for men and women, especially since the somewhat disconcerting results of the Women's Health Initiative have dampened enthusiasm for hormone replacement therapy in menopausal women. Bisphosphonates like alendronate (ALN) and risedronate have been demonstrated to have a favorable effect on bone mineral density (BMD) and fracture risk, mediated through decreased bone resorption. Parathyroid hormone (PTH) has been shown to have favorable anabolic effects on BMD, which could theoretically complement benefits accrued through antiresorptive therapy with bisphosphonates.

In this study of postmenopausal women with low BMD (T score = -2.0 or less) patients were randomly assigned to PTH (n = 119), ALN (n = 60), or the PTH + ALN combination (n = 59) for 12 months. PTH was administered as 100 µg SQ QD, ALN 10 mg QD, and all study participants received 500 mg calcium (Tums) and 400 IU of vitamin D.

BMD enhancement in the lumbar spine was similarly attained with PTH, ALN, or PTH + ALN. At the hip, ALN and ALN + PTH improved BMD, but PTH alone did not. Although intellectually appealing, the combination of an anabolic bone agent (ie, PTH) with an antiresorptive agent (ie, ALN) failed to provide meaningful benefit over either agent used alone. Whether these conclusions would apply to other bisphosphonates such as risedronate is uncertain, but these results would not encourage such combination treatment until more edifying results have been obtained. ■

Black DM, et al. N Engl J Med. 2003; 349:1207-1215.

Evaluation of D-Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis

All strategies currently used for the diagnosis of suspected deep-vein thrombosis (DVT) are imperfect. Since investigative tools are time-consuming, can produce false-positive results leading to unnecessary hospitalizations and treatments, and are responsible for some not-insubstantial costs, refinement of strategies to improve diagnosis without sacrificing accuracy are needed.

In step one of this trial, clinicians used a clinical model for predicting pretest probability of DVT. This model scored DVT probability based upon clinical characteristics such as presence of cancer, recent immobilization, leg swelling, and history of previous DVT.

In one group, patients (n = 601) considered unlikely to have DVT based upon clinical prediction model were randomized to either d-Dimer (DIM) testing or ultrasound imaging (USI). If the DIM was positive, USI was performed, but if negative, DVT was considered ruled out, and no USI was performed. Patients were followed for 3 months after presentation.

A second group (n = 495) who scored high on likelihood of having DVT were randomized to DIM + USI vs USI alone. Persons with negative USI but positive DIM underwent follow-up USI for DVT confirmation 1 week later.

Results indicated that in patients identified as low likelihood of DVT based upon a clinical model scoring system, a negative DIM essentially excludes the diagnosis. ■

Wells PS, et al. N Engl J Med. 2003; 349:1227-1235.

Exercise Testing to Predict Cardiovascular and All-Cause Death in Women

In the mid 1970s almost 3000 asymptomatic women underwent Bruce-protocol exercise treadmill tests (ETT) as part of the Lipid Research Clinics Prevalence study. These women had entered the trial due to elevated lipids, but were free of known cardiovascular disease at the time of their ETT. The short-term prognostic value of ETT in women has suffered some criticism, but little data have been available on long-term prognosis based upon ETT.

The mean follow-up was 20.3 years, during which time 14% of subjects died; cardiovascular deaths comprised 34% of all deaths. Women with highest exercise capacity on ETT had lower overall mortality rates, as well as cardiovascular deaths. For each MET decrease in exercise capacity at baseline, there was a 20% greater hazard ratio for cardiovascular death over the study observation period. On the other hand, ST segment changes did not predict subsequent cardiovascular death, in contradistinction to findings previously demonstrated in male populations. Data from ETT, specifically METs exercise capacity, is predictive of long-term cardiovascular mortality and might prove useful on a more large-scale population basis for risk stratification. ■

Mora S, et al. JAMA. 2003;290: 1600-1607.

A Subtle Reality Rhythm?

By Ken Grauer, MD

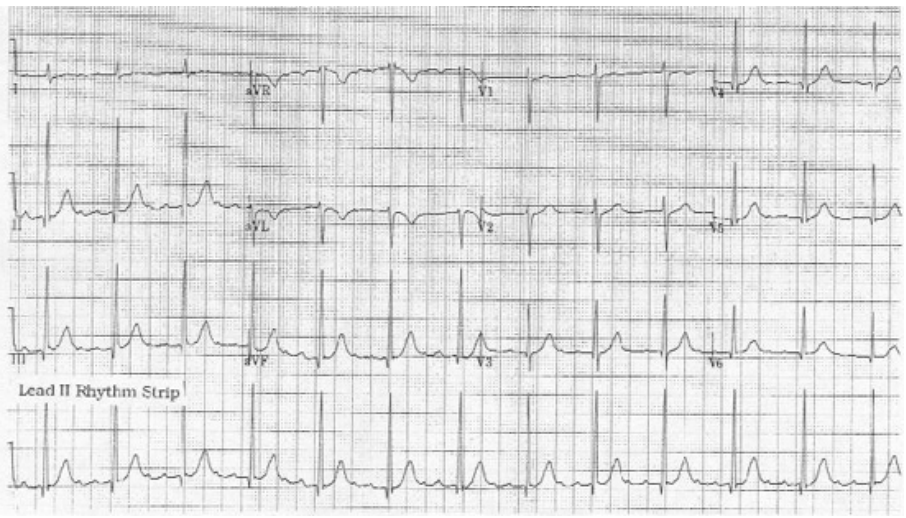

Figure. 12-lead ECG and rhythm strip obtained from a 74-year-old man with severe pulmonary disease.

Clinical Scenario: The 12-lead ECG and accompanying lead II rhythm strip in the Figure were obtained from a 74-year-old man with sever pulmonary disease. The computer interpreted this tracing as showing normal sinus rhythm. Do you agree?

Interpretation: This is a difficult tracing. There are actually *two* small upright deflections seen in lead II during the interval that extends from the end of the T wave until the next QRS complex. Each of these 1 mm deflections in lead II look alike. The distance between them is approximately one large box in duration, which would correspond to a rate of 300/minute if these deflections represented regularly occurring atrial activity. In favor of these subtle deflections being real (ie, not due to artifact) is the observation that they are seen in several leads at approximately the same point in the cardiac cycle. Thus, in addition to their consistent appearance throughout the lead II rhythm strip, these dual deflections are also seen in leads I, III, aVR, aVF, and V_3. This occurrence in multiple leads should suggest the possibility of atrial flutter. On the other hand, flutter waves generally tend to be larger in amplitude and typically manifest a "sawtooth" pattern, at least in the inferior leads and/or in leads V_1 and V_2. In addition, a suggestion of flutter activity in one or more leads is usually apparent throughout other points in the cardiac cycle. These can often be mapped out with calipers at a regular rate consistent with the rate of flutter activity. Other than the two deflections described above that occur between the end of the T wave and the next QRS complex, there is no definite indication of potential flutter activity in any other part of the cardiac cycle. This should raise the possibility of artifact (from body tremor or other reason) as the cause of these dual deflections identified in the leads we describe. Subsequent tracings on this patient however, confirmed that these subtle dual deflections did in fact represent flutter activity. The ECG and rhythm strip in the Figure are therefore an excellent example of how subtle atrial flutter can be! Clearly, definitive diagnosis of this rhythm can not be made by assessment of only the 12-lead ECG and rhythm strip shown in the Figure. Instead, diagnostic maneuvers (ie, carotid massage) and/or additional tracings are needed for diagnosis. Nevertheless, an extra deflection is present in several leads of this ECG, and recognition of this repetitive at a rate of approximately 300/minute should be enough to raise suspicion of atrial flutter and spur further investigation. ■

In Future Issues:

Antiviral Smallpox Vaccination

PHARMACOLOGY WATCH

Generic Paxil Scheduled to Hit Market this Fall

A generic form of paroxetine (Paxil—GlaxoSmithKline) will soon be on the market. The drug marks the second SSRI antidepressant to go generic after fluoxetine (Prozac) last year. US sales of Paxil reached $2.23 billion last year, and the approval of a generic is a blow to GSK's bottom-line but is welcome news to consumers. Generic paroxetine will be launched by Canadian drugmaker Apotex almost a year earlier than most analysts had anticipated because of continued legal wrangling over patents. If generic companies launch a drug that is later found in violation of the branded drugs patents, they are liable for treble damages, a threat that has impeded generic competition in the past. In this case, Apotex feels it has a strong legal basis for defending any claims by GSK, a pattern that is being seen more frequently among generic companies in the last year. Generic paroxetine should be available this fall in 4 different dosing strengths.

New Study Questions CHD and C pneumoniae

An association between *Chlamydia pneumoniae* infection and coronary heart disease has been suggested by several lines of evidence; however, a new, large, multicenter study fails to confirm this association. Nearly 8000 adults with a recent myocardial infarction and positive *C pneumoniae* titers were randomized to 12 weeks of azithromycin (600 mg/d for 3 days then 600 mg/wk through week 12) or placebo. The primary outcomes were death from any cause, nonfatal reinfarction, coronary revascularization, or hospitalization for angina. After a median of 14 months of follow-up, there was no significant risk reduction with azithromycin vs placebo (any primary event 7% risk reduction with azithromycin, P =.23). Adverse reactions to the study drug occurred in 13.2% of patients randomized to azithromycin and were generally mild—predominately diarrhea. The study represents the largest antibiotic trial to date for the eradication of *C pneumoniae*, and although there were indications that there might be an early benefit, this was not sustained at 14 weeks. The authors suggest that there's no justification for the use of antibiotics in treating patients with coronary disease (*JAMA*. 2003;290:1459-1466).

Warfarin Patients: Limit Cranberry Juice

Cranberry juice may increase the risk of hemorrhage in patients taking warfarin according to British researchers. The British Committee on Safety of Medicines recommended patients taking warfarin should limit or avoid drinking cranberry juice until they can sort out 5 reports of hemorrhage associated with the combination, including 1 death. In all cases, increases in INR were noted when patients who had been stabilized on warfarin started drinking cranberry juice. The committee postulates that the juice inhibits cytochrome P450 activity, thus slowing metabolism of warfarin. Cranberry juice has been touted in recent years for its antioxidant proper-

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ties as well as its purported ability to prevent or treat urinary tract infections.

Therapeutic Magnets Put to Test

A randomized double-blind trial has finally put therapeutic magnets to the test for the treatment of foot pain. Researchers at the Mayo Clinic randomized 101 adults with the diagnosis of plantar heel pain to treatment with cushioned insoles with bipolar magnets and sham magnets. The insoles were worn daily for 8 weeks. The main outcome was reported average daily for pain and the effect of the insoles on work performance and enjoyment. Again, at 8 weeks no significant difference was noted between the 2 groups, with both groups reporting significant improvements in foot pain (33% improvement nonmagnetic group, 35% improvement magnetic group [P = .78]). The authors conclude that embedded bipolar magnets to add nothing to cushioned insoles and the treatment of plantar heel pain (*JAMA*. 2003;290:1474-1478).

St. John's wort Might Block Certain Medications

St. John's wort, the popular herbal product that is widely used to self-treat depression may significantly reduce the effectiveness of at least 50% of all marketed medications. A new study looked at the effect of St. John's wort on cytochrome P450 (CYP) enzymes. Twelve healthy volunteers (6 men and 6 women) were given St. John's wort for 14 days. Participants were given dextromethorphan and alprazolam before and after administration of St. John's wort to assess plasma pharmacokinetics. After 14 days use of St. John's wort, a 2-fold decreased area under the curve for alprazolam plasma concentration and a 2-fold increase in alprazolam clearance was found as well as an elimination half-life that decrease from 12.4 h to 6.0 h suggesting a significantly induced activity of CYP 3A4 (all findings significant at $P <$ .001). Dextromethorphan metabolism, a measure of CYP 2D6, was unchanged. The effect of St. John's wort on CYP 3A4 is quite significant, however, since at least 50% of all medications currently on the market are at least partially metabolized by this enzyme. This, coupled with 2 recent multicenter double-blind, placebo-controlled studies questioning the effectiveness of St. John's wort for the treatment of depression, should alert clinicians to question their patients about their use of herbal medications, especially St. John's wort (*JAMA*. 2003;290:1500-1504).

Parathyroid Hormone and Alendronate Offer No Improved Osteoporosis Treatment

Parathyroid hormone and alendronate in combination offer no advantage and may in fact be less effective than either drug alone in treating osteoporosis according to 2 studies in the Sept. 25 issue of *New England Journal of Medicine*. In a study of 83 men with low bone density, 28 were randomized to receive alendronate 10 mg/d, 27 received parathyroid hormone 40 mg subcutaneously daily, while 28 men received both. The bone mineral density of the lumbar spine, proximal femur, radial shaft, and total body was measured every 6 months and trabecular bone mineral density of the lumbar spine was measured at baseline and 30 months. The most effective treatment was parathyroid hormone alone ($P < 0.001$ for both comparisons), and it appeared that alendronate impaired the ability of parathyroid hormone to increase bone mineral density at the lumbar spine and femoral neck. In the second study, 238 postmenopausal women with low bone mineral density at the hip or spine were randomly assigned to daily treatment with parathyroid hormone 100 mg/d (119 women), alendronate 10 mg/d (60 women), or both (59 women). After 12 months of follow-up, bone mineral density was assessed at the spine and hip. Bone mineral density increased in all treatment groups, but the volumetric density of trabecular bone in his spine increase substantially more in the parathyroid hormone group than either of the other groups. The authors suggest that there is no evidence of synergy between parathyroid hormone and alendronate and there may be evidence that alendronate reduces the anabolic effects of parathyroid hormone in the study group (*N Engl J Med*. 2003;349:1207-1215, 1216-1226).

FDA Actions

Barr laboratories has received approval to market an extended-cycle birth control pill that cuts the number of a women's menstrual cycles from 13 to 4 per year. Marketed under the trade name "Seasonale," the product is a 91-day ethinyl estradiol/levonorgestrel oral contraceptive regimen that includes 84 days of active hormones and 7 days of placebo. The new product seems to be as effective as other oral contraceptives; however, the label does note that the longer interval between menstrual periods may allow for unintended pregnancies to go undetected for longer period of time. ■