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Efficacy and Safety of Alosetron in Women with Irritable Bowel Syndrome

A B S T R A C T & C O M M E N T A R Y

Synopsis: *Alosetron was well tolerated and clinically effective in alleviating pain and bowel-related symptoms in this population of women with IBS.*

Source: Camilleri M, et al. *Lancet* 2000;355:1035-1040.

In this study, the efficacy of the new 5-ht3 receptor-antagonist alosetron was evaluated in 647 female patients with irritable bowel syndrome (IBS). Treatment with alosetron 1 mg b.i.d. or placebo was for 12 weeks followed by a four-week post-treatment period. The primary evaluation end point was adequate relief of pain and discomfort. Over the evaluation period, the drop-out rates were 24% and 16% for alosetron- and placebo-treated groups, respectively—the difference in drop-out rates being attributed to a higher rate of occurrence of constipation in the alosetron group. More patients in the alosetron group reported adequate relief at three months: 41% vs. 29%. Constipation occurred in 30% and 3% of the alosetron and placebo groups, respectively. Camilleri and colleagues conclude that alosetron was well tolerated and clinically effective in alleviating pain and bowel-related symptoms in this population of women with IBS.

COMMENT BY EAMONN M. M. QUIGLEY, MD

IBS remains a common and clinically challenging problem in primary care and subspecialty practices. There have been, however, significant advances in our understanding of the pathophysiology of this condition with visceral hypersensitivity and/or hyperalgesia attracting particular attention. Basic research has, in turn, revealed a significant role for serotonin (5-HT)-receptors, and the 5-HT3-receptor in particular, in the mediation of visceral sensation. Several antagonists to this receptor have been developed for, and tested in, functional bowel disorders; alosetron is the first to enter clinical practice and represents, therefore, a new departure in the therapy of IBS. How good is it? As this, and prior studies have demonstrated, alosetron is consistently and significantly superior to placebo in

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INSIDE

relieving pain and discomfort; two of the cardinal symptoms of IBS. Though the therapeutic gain may, at first sight, appear modest it must be viewed in the context of a disorder where quotable P values are a distinct rarity in clinical trials! Alosetron may not suit all patients; studies to date have shown efficacy only in females and especially in those with the somewhat less common diarrhea-predominant variety of the disorder. As illustrated by this study, constipation is a significant side effect issue and its use is probably inadvisable in those with a constipation-predominant form of IBS. How about its efficacy among those with what is, perhaps, the most common manifestation, namely, the "alternator," who alternates between diarrhea and constipation? We await the outcome of clinical trials. Comparisons with tricyclic and serotonin reuptake inhibitor classes of antidepressants as well as simple anti-diarrheals will also be of interest. ❖

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Dizziness: A Geriatric Syndrome

ABSTRACTS & COMMENTARY

Synopsis: *Dizziness may often be multifactorial in origin and, as such, is similar to other "geriatric syndromes" such as falling, delirium, and urinary incontinence.*

Sources: Tinetti ME, et al. *Ann Intern Med* 2000;132: 337-344; Drachman DA. *Ann Intern Med* 2000;132:403-404.

Tinetti and colleagues studied 1087 community-living elderly persons to determine the predisposing characteristics and situational factors associated with dizziness. Dizziness was categorized into four groups of symptoms: loss of balance, near-fainting, spinning or movement, and other or multiple sensations. Tinetti et al used an interview and questionnaire to assess medical history and symptoms, standard tests such as the mini-mental state exam, and psychiatric inventories to assess cognition, effect, and anxiety state. Physical examinations were limited to screening tests of blood pressure, balance, and hearing. Of the participants, nearly one-quarter (261; 24%) reported long-term recurrent episodes of dizziness. More than half of dizzy persons (56%) described several sensations and almost three-quarters (74%) reported several positions or activities that were associated with the occurrence of dizziness. Getting up from either lying down or sitting, turning either the head or the entire body, and being upset or anxious were the most frequently reported triggering activities.

Seven characteristics were associated with dizziness: anxiety, depression, impaired balance, previous myocardial infarction (MI), postural hypotension, five or more medications, and impaired hearing. The more of these characteristics that elderly patients had, the more likely they were to report dizziness. Tinetti et al conclude that dizziness may often be multifactorial in origin and, as such, is similar to other "geriatric syndromes" such as falling, delirium, and urinary incontinence.[1,2]

In an accompanying editorial, Drachman agrees with Tinetti et al that dizziness, especially among the elderly, is often due to multiple disorders involving multiple organ systems. He recalls the "all-too-familiar dizzy patient who has cataracts, hearing loss, peripheral neuropathy, cervical spondylosis, and atrial fibrillation and takes a number of medications for these conditions."

Drachman also points out that the questions asked and screening tests used by Tinetti et al in their epidemiologic study are not the way physicians, especially neurolo-

gists, diagnose the cause of dizziness in patients. The physician must sort out the diagnosis by taking a detailed history to identify specific and distinctive symptoms and then perform a physical examination that evaluates cognition, vision, vestibular function, coordination, peripheral sensation, and motor functions.

Finally, Drachman fears that identifying dizziness as a "geriatric syndrome" may suggest not only that multiple problems can produce the symptoms, but also that it is just another undiagnosable and untreatable condition of old age.

COMMENT BY JOHN J. CARONNA, MD

Equilibrium and stability result from interactions among multiple organ systems. Therefore, it is not surprising that Tinetti et al found an association between multiple predisposing factors and dizziness. In their study, both depressive symptoms and antidepressant drugs were associated with dizziness. Furthermore, the strong relation between numbers of medications and dizziness supports the need to review the possible role of medication side effects in patients who have dizziness.

The study supports a comprehensive approach to the dizzy patient and suggests that clinicians should not only seek to diagnose one discrete cause for dizziness but also try to identify potentially treatable contributing factors. (*Dr. Caronna is Vice-Chairman, Department of Neurology, Cornell University Medical Center, Professor of Clinical Neurology, New York Hospital, New York, NY.*) ❖

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Combination Therapy with Metformin-Rosiglitazone vs. Metformin Alone

ABSTRACT & COMMENTARY

Synopsis: *Combination treatment with rosiglitazone and metformin improved glycemic control, insulin sensitivity, and beta cell function more effectively than treatment with metformin alone.*

Source: Fonseca V, et al. *JAMA* 2000;283:1695-1702.

Most antidiabetic agents attack only one of several causes of diabetes. Metformin promotes glucose lowering by reducing hepatic glucose production and gluconeogenesis and by enhancing peripheral glucose uptake. Rosiglitazone promotes glucose transporters and activating adipocyte differentiation.[1] Fonseca and colleagues evaluated the efficacy of metformin-rosiglitazone therapy in patients whose type 2 diabetes was poorly controlled with metformin alone.

This was a randomized, double-blind, placebo-controlled trial in 36 outpatient centers in the United States. A total of 348 patients aged 40-80 years with a mean fasting glucose of 216 mg/dL, a mean glycosylated hemoglobin of 8.8%, and a mean body mass index of 30.1 kg/m^2 were randomized.

Patients received 2.5 g/d of metformin plus placebo, 2.5 g/d of metformin plus 4 mg/d of rosiglitazone, 2.5 g/d metformin, and 8 mg/d rosiglitazone.

Glycosylated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and beta-cell function improved significantly with the metformin-rosiglitazone therapy in a dose-dependent manner. The mean glycosylated hemoglobin decreased by 1% in the 4 mg/d rosiglitazone group and 1.2% in the 8 mg/d rosiglitazone group. Of patients receiving the 8 mg/d dose of rosiglitazone, 28.1% achieved a glycosylated hemoglobin of less than 7%. Dose-dependent increases in body weight and total and low-density lipoprotein cholesterol levels were observed in both rosiglitazone groups vs. placebo.

The data suggested that combination treatment with rosiglitazone and metformin improved glycemic control, insulin sensitivity, and beta cell function more effectively than treatment with metformin alone.

COMMENT BY RALPH R. HALL, MD, FACP

The conclusion printed in the original article in *JAMA* stated that this benefit occurred with once-daily metformin-rosiglitazone therapy. I could not believe that the metformin could be given in this dose once daily without substantial side effects. A telephone call to Dr. Fonseca confirmed that this was an error in the editing. She indicated that the metformin had been given in multiple doses as it should have been.

This is a carefully conducted study that points to the usefulness of this combination of anti-diabetic drugs. The study was carried out over a 26-week period of time for the drug combination. HbA_{1C} levels in the rosiglitazone groups decreased after four weeks and plateaued by week 18. It was noted that the HDL cholesterol decreased to an extent that the ratio of HDL to LDL cholesterol did not change. Of particular interest is that no one in the rosiglitazone group experienced elevations in the alanine amino transferase. There is still

concern, however that if rosiglitazone is used in enough patients that liver problems will be identified.

It is also of note that in a smaller study of patients (less well conceived from a statistical point of view) treated with metformin and repaglinide with slightly lower baseline levels of blood glucose, that the HbA_{1C} levels fell 1.4%.[2] Repaglinide acts by stimulating insulin release by slightly different mechanisms than the sulfonylureas. We, therefore, have a number of combinations available for patient treatment. However, in order to reach the desired goal of a HbA_{1C} of less than 7%, a third oral drug or insulin would have been needed in more than two-thirds of the patients in this study.

The big question today is can we prevent beta cell failure by more intensive treatment earlier in the course of the disease? Does glucose toxicity cause permanent damage to the beta cell if present for only a few months? Should we start combination therapy without a trial of exercise and diet in order to prevent permanent damage? A number of investigators believe this to be a distinct possibility. ❖

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Maintenance Methadone Better than Quick Detox with Prolonged Psychosocial Activities for Opiate-Dependent Patients

ABSTRACT & COMMENTARY

Synopsis: *In treatment of opiate-dependent individuals, prolonged methadone maintenance does better than quick methadone withdrawal with 180 days of psychosocial detoxification.*

Source: Sees KL, et al. *JAMA* 2000;283:1303-1310.

Despite the increase in cocaine abuse in the United States over the last 20 years, admissions to treatment programs for opioid dependency (heroin, etc.) surpassed the cocaine admissions in the United States in 1997. This has prompted the U.S. Department of Health and Human Services to consider changing the policy of federally registered methadone clinics in the United States. These changes would allow private or group practice physicians to provide opiate treatment outside methadone maintenance clinics. This in part may have been a response to a recent consensus conference that called for integrating substance abuse services into primary care in the United States.

Thus, there exists a significant impetus for a research on detoxification programs, possibly shortened by enhanced psychosocially enriched counseling. Sees and colleagues did just this.

Sees et al compared the outcomes of opiate-dependent patients treated with standard methadone maintenance therapy provided by a federally registered methadone maintenance clinic to an alternative treatment consisting of psychosocially enriched 180-day methadone assisted detoxification. This randomized, controlled trial consisted of 858 volunteers being screened and 179 adults being randomized. A total of 154 adults completed the 12 weeks of follow-up.

Ninety-one patients were randomized to methadone maintenance therapy (MMT), which in their study required two hours of psychosocial counseling during the six months of the study. Eighty-eight patients were randomized to detoxification requiring three hours of psychosocial counseling including 14 education sessions and an hour of group cocaine therapy (if they answered yes to cocaine abuse questions or tested positive for cocaine in the urine), with an additional six months of services provided afterward. In the detox program, the methadone was reduced rapidly over 60 days after 120 days of stabilization.

Sees et al found a higher treatment retention rate (438 vs 174) and lower heroin use in the MMT group than in the detox group. MMT also resulted in a lower rate of drug-related HIV risk behavior, but interestingly not a lower sex-related HIV risk behavior. Also looked at were employment, family functioning, and alcohol abuse, and no differences were found. The MMT group stayed in treatment longer. Neither group showed any difference in their illicit opioid use. The MMT group had a precipitous decline in heroin use, needle-related HIV risk behavior, and drug-related crimes.

Fifty percent of the patients in both groups used heroin at least once during any month in the treatment, cocaine use (among those at risk), sex-related HIV risk behaviors, employment problems, and family problems persisted despite either program.

COMMENT BY LEN SCARPINATO, DO, FACP, FCCP

There has been a movement to limit the effect of

methadone treatment centers by creating programs that are shorter in time, more intense in therapy, and possibly available at family care offices. The idea being that you can reduce methadone length of treatment by providing more psychosocial counseling. This study by Sees et al shows us that we can't exactly do that. For the important parameters listed above, methadone maintenance therapy beat out the shorter version with more psychosocial counseling. Yet we have a long way to go when 50% are still using heroin once a month!

As a primary care physician who sees this dependency in a correctional medicine facility or my family practice setting, this study has important implications. I can't just patch together an opioid withdrawal clinic "without walls." I would have to involve multiple services and increased psychosocial counseling, and not do better than MMT. What is needed is methadone (or other alternatives also discussed in this issue of *JAMA*). In a related editorial, Rounsaville and Kosten discuss another article by Weinrich and Stuart in the same issue of *JAMA*.[1,2] This article discusses primary care physicians using methadone.[2] Weinrich and Stuart report a 3- to 5-fold increase in the proportion of patients served secondary to a supervised methadone consumption program in a primary care clinician's office. This may be the future in the United States, especially if the U.S. officials decide to take the consensus to heart. ❖

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Pharmacology Update

Rivastigmine Tartrate Capsules and Oral Solution (Exelon—Novartis)

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

Rivastigmine was recently approved by the FDA for the treatment of mild to moderate dementia of the Alzheimer's type. It is a cholinesterase inhibitor similar to tacrine and donepezil. Rivastigmine is marketed as capsules and an oral solution by Novartis as Exelon.

Indications

Rivastigmine is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

Dosage

The recommended starting dose is 1.5 mg twice a day with food. If the drug is tolerated after a minimum of two weeks, the dose may be increased to 3 mg twice daily, then increased again, if tolerated, to a maximal dose of 6 mg twice daily. If side effects such as nausea, vomiting, abdominal pain, or loss of appetite occur, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose.[1] The solution may be administered directly from the dosing syringe or mixed with a small glass of water, cold fruit juice, or soda.

Rivastigmine is supplied as capsules (1.5 mg, 3.0 mg, 4.5 mg, 6 mg) and an oral solution (2 mg/mL, 120 mL). An oral syringe is provided to measure the appropriate dose.

Potential Advantages

Cytochrome P450 isoenzymes are minimally involved in the metabolism of rivastigmine.[1] Drug-drug interactions involving rivastigmine and drugs metabolism by the cytochrome P450 system are not expected. Tacrine and donepezil are metabolized by the P450 system.

Potential Disadvantages

Rivastigmine's side effects are similar to other cholinesterase inhibitors and include nausea, vomiting, anorexia, and weight loss. In the controlled trials, 47% of patients taking 6-12 mg/d developed nausea compared to 12% for placebo. Other side effects compared to placebo: 31% had one episode of vomiting vs. 6%, 26% weight loss (≥ 7% of baseline weight) vs. 6%, and 17% anorexia vs. 3%.[1] These side effects generally occur during the titration period and tend to be less severe during the maintenance phase.

In the 26-week trials, 65-67% of patients completed the study at the high dose compared to 84% for placebo and 85% for the low dose (1-4 mg/d).

Fifteen percent of patients discontinued due to side effects.[1]

Rivastigmine requires twice daily dosing compared to once daily for donepezil.

Comments

Rivastigmine is the third cholinesterase inhibitor to be approved for the treatment of Alzheimer's disease (AD). In contrast to tacrine and donepezil, which are

reversible shorting-acting drugs, rivastigmine is a "pseudo irreversible intermediate-acting" drug and can inhibit the enzyme up to 10 hours even though it has an elimination half-life of about 1.5 hours.[1,9] Donepezil has an elimination half-life of 70 hours permitting once-daily dosing compared to twice daily for rivastigmine.

The safety and efficacy were assessed in 26-week trials, one in the United States (n = 699) and the other in Europe and North America (n = 725).[2-4] In these trials, patients with probably mild to moderately severe AD were randomized to receive 6-12 mg/d or 1-4 mg/d of rivastigmine or placebo. There was a 12-week forced titration phase and a 14-week maintenance phase. Efficacy was assessed using the cognitive subscale of the AD assessment scale (ADAS-Cog) and the Clinician Interview Based Impression of Change Scale (CIBIC-Plus), and progressive deterioration scale. The ADAS-Cog is a 70-point scale that assesses memory language, orientation, and praxis. The CIBIC-Plus is a 7-point scale incorporating caregiver information and measuring global assessment of behavior, general psychopathology, cognition, and activities of daily living. The progressive deterioration scale, which is not an indicator of efficacy recognized by the FDA, assesses activities of daily living including dressing, eating independently, social interaction, participation in housework and hobbies, awareness of time, and handling financial matters. Results showed a modest improvement in cognitive testing and clinical impression of change and participation in daily living. The change in ADAS-Cog was 2.6-4.9 U and 0.35-0.41 in CIBIC-Plus for the 6-12 mg dose compared to placebo. The mean score in the progressive deterioration scale improved from baseline in the high-dose group. The 1-4 mg/d dose was generally not effective. The magnitude of effect appears similar to that reported for donepezil.[4,5] In terms of side effects, the 5 mg dose of donepezil may be better tolerated than the 6-12 mg dose of rivastigmine. The two products are priced identically, $4.35 per day, with each strength having the same price. A comparative trial between rivastigmine and donepezil is expected to be initiated by the end of the year.[6]

Clinical Implications

It is estimated that one in 10 persons older than the age of 65 and nearly half of those older than 85, or about 4 million persons in the United States, have AD.[7] There are currently no treatments that stop or reverse the progression of the disease. Rivastigmine, as with donepezil, produces modest benefit in cognitive testing and clinical impression of change. Their effect on improved functional ability is less clear.[8] ❖

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CME Questions

34. Which one of the following statements is true?

a. Metformin acts by inhibiting hepatic glucose production and increasing peripheral glucose uptake.
b. Rosiglitazone acts by increasing insulin release.
c. By using a combination of metformin and rosiglitazone 100% of patients with type 2 diabetes can obtain a HbA_{1C} level of less than 7%.

35. Dizziness in the elderly is "a geriatric syndrome" because:

a. it is a normal part of aging.
b. it is undiagnosable and untreatable.
c. it is often the product of multiple conditions.
d. None of the above
e. All of the above

36. Which one of the following statements is *not* correct?

a. Rivastigmine requires twice daily dosing compared to once daily dosing for donepezil.
b. Rivastigmine is supplied as capsules and an oral solution.
c. Rivastigmine has no side effects in patients.
d. Rivastigmine is a cholinesterase inhibitor similar to tacrine and donepezil.

By Louis Kuritzky, MD

Monitoring Osteoporosis Therapy with Bone Densitometry: Misleading Changes and Regression to the Mean

Bone mineral density (bmd) is often used as a surrogate marker of efficacy for osteoporosis treatments. Cummings and colleagues evaluated whether the small number of women who are reported to lose BMD during treatment with an active agent (alendronate or raloxifene, in this case) are indeed losing BMD, which should be consistent and continuous over time, or whether, with continued monitoring, these women would tend to regain bone mass, indicative of a regression to the mean (RTM) type effect.

Study subjects (n = 6588) were composed of participants in the Fracture Intervention Trial and Multiple Outcome of Raloxifene Evaluation trial. Subjects had to have completed two years of treatment in the trials. Outcomes measured were hip and spine BMD at baseline, 12, and 24 months.

On average, treatment resulted in an increase of 2.2% in the hip and 4.5% in the spine BMD at the end of year 1. Of women who lost BMD during year 1, those with the greatest loss showed the steepest slope of increase BMD during year 2. Cummings et al comment that indeed individuals who have measurements disparate from the mean tend to demonstrate RTM effect when followed for longer time periods. One conclusion to be drawn is that treatment of osteoporosis with pharmacotherapy may still be continued even in persons who initially lose BMD, as most will reverse this trend with continued therapy. ❖

Cummings SR, et al. JAMA 2000;283: 1318-1321.

Risks of Untreated Isolated Systolic Hypertension in the Elderly

The ascendancy of systolic blood pressure over diastolic as a predictor of adverse cardiovascular outcomes has only recently been popularized. Most recent meta-analyses have focused upon large accumulated data derived from prospective randomized trials that used diastolic blood pressure as the primary measurement tool. In the last decade, three large randomized trials of treatment for isolated systolic hypertension have each demonstrated cardiovascular risk reduction. The large amount of patient experience generated by these trials allows for commentary based upon a meta-analysis of trials limited to systolic hypertension.

Staessen and colleagues included older patient populations (age > 60) with isolated systolic hypertension from the SHEP, Syst-Eur, and the Syst-China trials. Additionally, persons with isolated systolic hypertension that participated in the EWPHE, HEP, STOP, MRC-1, and MRC-2 trials were included in the analysis.

Assessing data of these trials for patients followed for a median of 3.8 years (n = 15,693) demonstrated a total mortality reduction of 13%, cardiovascular mortality reduction of 18%, stroke reduction of 30%, and coronary event reduction of 23%. These favorable effects of treatment are similar to those achieved in the large body of diastolic based hypertension trials. This meta-analysis concludes that treatment of isolated systolic hypertension is of substantial benefit in older patients. ❖

Staessen JA, et al. Lancet 2000;355: 865-872.

Ciprofloxacin and Trimethoprim-Sulfamethoxazole for Acute Uncomplicated Pyelonephritis in Women

Randomized trials were able to establish that the traditional 10- to 14-day therapy used for lower urinary tract infection (i.e., uncomplicated cystitis in women) may be safely accomplished with as little as three days of appropriate therapy. Pyelonephritis is responsible for a substantial number of hospitalizations, with the traditional regimen being 14 days, with no randomized trials confirming efficacy of shorter regimens. Increasingly complex patterns of antimicrobial resistance, hospital use patterns, and cost efficacy monitoring support a trial to compare therapies for acute uncomplicated pyelonephritis (APN).

Subjects with APN (n = 378) were randomly assigned to treatment with either one week of ciprofloxacin 500 mg b.i.d. or two weeks trimethoprim-sulfamethoxazole 160/800 mg b.i.d.

The clinical cure rate for ciprofloxacin was statistically superior to that of trimethoprim-sulfamethoxazole (96% vs 83%). Adverse drug effects occurred to a similar degree among both groups, though there was a trend to more adverse effects among trimethoprim-sulfamethoxazole recipients. This study demonstrates the superiority of seven days of ciprofloxacin for APN, but results must be viewed as only applicable to women, since no men were included in the trial, and the pathology of APN in men may reflect both different pathogens and different etiologic factors resulting in APN. ❖

Talan DA, et al. JAMA 2000;283: 1583-1590.

ECG Review

How Many PACs?

By Ken Grauer, MD

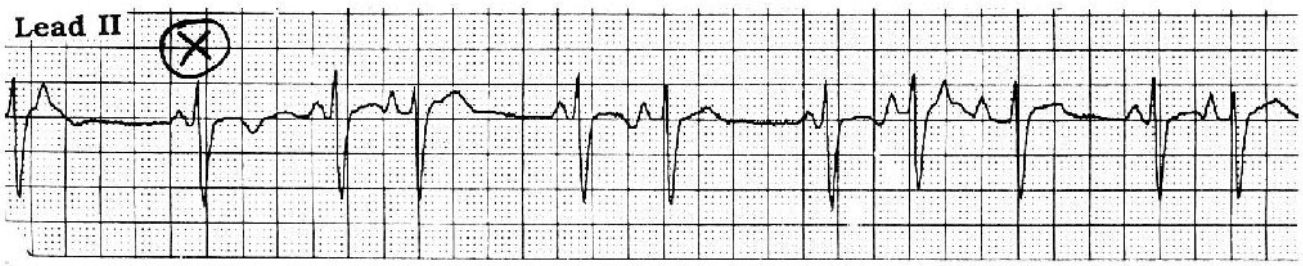

Figure. Rhythm strip showing PACs. How many PACs are there?

Clinical Scenario: The rhythm strip shows premature atrial contractions (PACs). *How many* PACs are seen on this tracing?

Interpretation: This is a tricky tracing to interpret. The starting point (and perhaps the most difficult part of the interpretation) is to determine what an *unaffected* sinus beat looks like. We propose that the beat marked X represents the *only* such unaffected beat on the tracing. Note that this beat manifests a rounded (coved) ST segment with a shallow, symmetrically inverted T wave. All other T waves on this tracing are distorted by premature P waves (PACs). Many of these PACs are blocked—some subtly (producing slight peaking in the T wave of the 4th, 6th, 9th, and 11th beats)—with other blocked PACs being much more obvious (note peaked PACs in the T waves of the very first beat on this tracing, as well as for the 8th beat). In all, we count a total of 11 PACs—but expect that others might not quite count the same. The answer is, therefore, that there are *a lot* of PACs on this tracing, with slight variation in their time of occurrence accounting for the continual change in ST-T wave morphology (due to superposition of these PACs on the normal T wave, which is negative in this lead). ❖

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