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Who Put the Die in Diastolic?

ABSTRACT & COMMENTARY

Synopsis: *Systolic blood pressure is a better predictor of cardiovascular and coronary heart disease mortality in men being treated for hypertension than is diastolic blood pressure.*

Source: Benetos A, et al. *Arch Intern Med.* 2002;162:577-581.

BENETOS AND COLLEAGUES RECRUITED 4714 HYPERTENSIVE men between 1972 and 1988 at the Centre d'Investigations Preventives et Cliniques in Paris. Supine blood pressure was carefully and manually measured, as were standard cardiovascular risk factors including tobacco use, diabetes, and serum cholesterol. Mortality data were collected an average of 14 years (range, 9-25) later for this cohort (through 1997). Control of hypertension was considered to be a systolic blood pressure below 140 mm Hg and a diastolic blood pressure below 90 mm Hg. Subjects were also stratified by levels of systolic and diastolic blood pressure to assess the effect of each. Relative risk (RR) and confidence intervals (CI) were calculated controlling for age, cholesterol, smoking, and diabetes. The RR of systolic blood pressure was calculated controlling for diastolic blood pressure, and vice versa.

The mean age of the group was 52 years. Mean blood pressure was 152/94 mm Hg. Only 14.5% of the patients had controlled values for both systolic and diastolic blood pressure, but systolic blood pressure was more likely (10.8 %) to be uncontrolled than was diastolic pressure (4.2 %). Those with uncontrolled blood pressure had increased RR for cardiovascular mortality (1.66; CI, 1.04-2.64) and coronary heart disease (CHD) mortality (2.35; CI, 1.03-5.35) compared to those with controlled blood pressure.

There was a linear relationship between systolic blood pressure and both cardiovascular and CHD mortality. Those with systolic blood pressure between 140 and 159 mm Hg had an age-adjusted cardiovascular mortality RR of 1.69 (CI, 1.03-2.76) and CHD RR of 2.54 (CI, 1.08-5.96) compared to those with systolic blood pressure below 140 mm Hg. The adjusted RRs for cardiovascular and CHD mortality in those with a systolic blood pressure of 160 mm Hg or more compared with those who had a systolic blood pressure below 140 mm Hg were 2.52 (1.56-4.09) and 3.51 (1.51-8.2), respectively.

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INSIDE

The increased risk of cardiovascular mortality was significantly higher in those with systolic blood pressure higher than 140 compared with those with systolic blood pressure under 140 after controlling for age, for the other cardiovascular risk factors, and for diastolic blood pressure. With regard to diastolic blood pressure, however, the relationship between diastolic blood pressure and cardiovascular mortality was not significant after adjusting for age, other associated risk factors, and systolic blood pressure.

Pulse pressure had essentially the same cardiovascular and CHD mortality predictive value as did systolic blood pressure.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

For at least 30 years, evidence has been accumulating that systolic blood pressure is a better indicator of cardiovascular risk than is diastolic blood pressure.[1,2] Indeed, the National High Blood Pressure Education Program has recently recommended that systolic blood pressure be the main criterion for the diagnosis, staging, and treatment of older Americans.[3] Isolated systolic hypertension is the most prevalent kind of hypertension in the general population,[4] and is also the most difficult to control.[5] Indeed, a companion article to the one under discussion documented that systolic blood pressure control was much less frequent than diastolic blood pressure control (29.9% vs 41.5%) both in the office and at home.[6] Not only does uncontrolled systolic blood pressure predict increased cardiovascular risk (unlike diastolic blood pressure), effective treatment of isolated systolic hypertension has been shown to dramatically reduce the risk of myocardial infarction, heart failure, and stroke.[5,7] We simply have got to do a better job of treating systolic hypertension. ■

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Oral Contraceptives and the Risk of Myocardial Infarction

ABSTRACT & COMMENTARY

Synopsis: *Third-generation oral contraceptives may be associated with less cardiovascular morbidity than first- and second-generation OCs.*

Source: Tanis BC, et al. *N Engl J Med.* 2001;345:1787-1793.

BECAUSE THE LITERATURE HAS BEEN CONTRADICTORY regarding the risk of myocardial infarction (MI) and which progestin is contained in an oral contraceptive (OC), this group from The Netherlands performed a retrospective, case-control study, called the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO).

RATIO enrolled women aged 18-49 years who presented to 1 of 16 centers with their first MI between January 1990 and October 1995. They were identified by searching hospital discharge databases for acute MI diagnosis codes. To qualify as an acute MI, the patient had to be symptomatic and have elevated cardiac enzymes and electrocardiographic changes. Three hundred twenty-one (321) women were identified. Of these 29 were excluded, 28 who died and 1 who could not participate. Of the remaining 292, 21 could not be found and 23 chose not to participate. This left 248 women.

The control group contained 925 women, stratified by age, who were recruited by random-digit dialing in 6 geographic areas corresponding to where the patients lived. Women who had a history of coronary, cerebral, or peripheral vascular disease were excluded. They were questioned about demographics, weight, height, reproductive history, menopausal status, level of education, family history of cardiovascular disease, hypertension, diabetes, hypercholesterolemia, alcohol use, tobacco use, and use of OCs. Tanis and colleagues grouped the OCs by generation and estrogen content. Because the gene mutations factor V (Leiden) and G20210A in the prothrombin gene have been associated with MI in young women, Tanis et al tested blood or buccal swab samples from 217 patients and 763 controls for these.

The patients were older than the controls (42.7 vs 38.1 years). As expected, the patients were more likely to be hypertensive, hypercholesterolemic, and diabetic. They smoked more and had a lower level of education. Their families were more likely to be afflicted with cardiovascular disease. There was no difference in menopausal status. After demographic analysis, 3 patients and 9 controls were excluded for using hormone replacement therapy or because the researchers could not be sure they had used OCs.

Of the remaining 245 patients, 99 (40%) had used OCs of any generation. Of the remaining 916 controls, 348 (38%) had used OCs. The odds ratio (OR) for MI among OC users, after adjustment, was twice that of nonusers. When the ORs were calculated based on which generation of OCs were used, the results were 2.8 (confidence interval [CI], 1.3-6.3) for first-generation, 2.4 (CI, 1.6-3.6) for second-generation, and 1.3 (CI, 0.8-2.3) for third-generation OCs.

The amount of estrogen did not seem to affect the results. When Tanis et al compared women who used second-generation OCs with levonorgestrel and either 35 µg or 50 µg of ethinyl estradiol, the ORs were 2.6 (CI, 1.6-4.2) and 2.0 (CI, 0.6-7.3), respectively, a nonsignificant difference.

The traditional cardiovascular risk factors of smoking (OR, 7.9; CI, 4.9-12.9), hypertension (OR, 5.1; CI, 2.9-8.8), hypercholesterolemia (OR, 3.3; CI, 1.6-6.8), diabetes (OR, 4.2; CI, 1.6-10.9), and obesity (OR, 3.4; CI, 2.2-5.3) all increased the chance of MI among nonusers. Among OC users, the ORs were even higher: smoking (13.6), hypertension (6.1), hypercholesterolemia (24.7), diabetes (17.4), and obesity (5.1). The presence of either gene mutation did not increase the risk.

COMMENT BY ALLAN J. WILKE, MD

Almost all OCs have ethinyl estradiol as their estrogen component, except for a handful that contain mestranol. Estrogen-containing OCs are divided into 3 generations, based on their progestin content. First-generation OCs contain lynestrenol (not available in the United States) or norethindrone (for example, Brevicon®, Modicon®, Norinyl 1/35®, and Ortho-Novum 1/35®). Second-generation OCs contain norgestrel (Lo/Ovral®, Ogestrel-28®) or levonorgestrel (Alesse®, Tri-Levlin®, Triphasil®). Third-generation OCs contain desogestrel (Desogen®, Ortho-Cept®) or gestodene (not available in the United States). Some authorities include norgestimate (Ortho-Cyclen®, Ortho-Tricyclen®) as a third-generation OC, but Tanis et al did not. The third-generation OCs were marketed as being safer because of their favorable effect on lipid profiles. HDL cholesterol levels tended to be higher. In evidence-based medicine circles, this is known as disease-oriented evidence. Having a more favorable lipid profile may eventually prove to be a good thing, but it is premature to conclude that third-generation OCs are safer until we can look at "patient-oriented evidence that matters." This study is a first, hesitant step in that direction.

We have known about the association of OCs and MIs for almost 40 years. Over the years, attempts have been made to make them safer. Since we assumed that the main culprit was the estrogen component, we first reduced the amount of estrogen in each pill. As this study shows, reducing the estrogen content does not seem to reduce the risk; if anything, the ORs favored the higher 50-µg dose (statistically not significant). We then changed the progesterone component. The third-generation OCs have been associated with a small increase in the risk of venous thromboembolism (VTE). Indeed, Tanis et al just published a meta-analysis showing an increased risk of VTE with third-generation OCs.

As this is a retrospective, case-control study, we must examine its methods closely. The main concern is whether the patients and the controls were well matched. Are there unknown differences that distinguish the 2 groups? Other secondary concerns are the search strategy, the possibility of recall bias, and the definition of MI.

Their search strategy potentially missed women who had MIs and either died or did not present to the hospital. Tanis et al relied on women's memory of what OC they took (augmented by color photographs of available OCs). The definition of MI used in this study is strict; most practitioners in the United States would accept 2 of the 3 criteria as diagnostic. It could exclude diabetic patients who had a "silent" MI.

As with any report, it is prudent to compare your population with that of the study. These women were predominantly white (94% patients and 93% controls). Interestingly, they were not particularly well educated. Among the patients, 53% did not get beyond primary school (30% for controls) and only 10% of patients and 27% of controls had attended postsecondary school. This runs counter to my image of the Dutch. They were not extraordinarily obese (BMI = 25.7 for patients and 23.5 for controls), but they smoked like chimneys. Fully 84% of patients and 43% of controls were current smokers; Toledo, Ohio, my stomping grounds, is the smoking capital of metropolitan United States, and we are at only 31%.

I found it frustrating that Tanis et al did not "show their math" as they adjusted their data when calculating the ORs. The ratios may be legitimate, but I could not calculate them using the raw data in the tables. This makes accepting Tanis et al's conclusions rather like a matter of faith.

Let us put things into clinical perspective. Among all people younger than 25 years in the United States, the risk of death from an acute MI is 0.1 per 100,000 population. For 25-to-34-year-olds it is 1.3, and for 35-to-44-year-olds it is 7.8. Compare this to risk of death related to pregnancy among American women. For women younger than 20 years old, it is 8.5 per 100,000 live births. Similarly, for 20-to-29-year-olds, 30-to-34-year-olds, and 35-to-39-year-olds, the numbers are 9.3, 11.9, and 21.1, respectively. In other words, even with a doubling of the MI rate (as purported by this article), it is much more dangerous to be pregnant than to use OCs, provided none of the traditional risk factors are present. In a study of causation, you want the ORs to be large. The ORs for MI between the various generations are small, 1.3-2.8. Byway of comparison, the ORs for OCs and smoking, hypercholesterolemia, and diabetes are greater by an order of magnitude.

The risk of MI is not the first thing I worry about when I prescribe an OC. When I prescribe these drugs, I am usually trying to prevent a pregnancy, normalize a menstrual cycle, or control acne. My risk-benefit considerations include the risk of pregnancy, the risk of deep vein thrombosis, and the risk of exacerbating an estrogen-sensitive neoplasm. I ask about migraine, hypertension, and family history. As Tanis et al argue, since OCs are essentially equivalent in their effectiveness, safety should drive our prescribing habits. Among OCs, the third generation appear to be the safest regarding MI. They may be less safe for venous thromboembolism. We will have to wait until later publications to learn about how safe they are in cerebral infarction and peripheral artery disease. ■

Antioxidants—Yes or No?

ABSTRACT & COMMENTARY

Synopsis: *There is no clear evidence that antioxidants provided by dietary intake or by the addition of oral agents in the form of vitamin supplements can reduce the risk of developing atherosclerosis.*

Source: McQuillan BM, et al. *J Am Coll Cardiol.* 2001;38(7): 1788-1794.

Preventative therapies aimed at reducing the incidence of cardiovascular diseases, the single major cause of mortality and morbidity worldwide, have improved dramatically over the past decade. For many years, substantial interest has been focused on the potential benefits of antioxidant vitamins in cardiovascular disease prevention.

McQuillan and his associates from the Heart Research Institute of Western Australia studied 1111 subjects (558 men and 553 women) whose mean age was approximately 52 years by measuring dietary vitamin intake, fasting plasma levels of vitamins A, C, and E, lycopene, and alpha- and beta-carotene. In addition, they performed bilateral carotid artery B-Mode ultrasound imaging. After adjustment for age and conventional risk factors, they found a progressive decrease in intima-media wall thickness (IMT). Dietary vitamin E levels accounted for only 1% of the variants in measured IMT in men and, in fact, there was an inverse association between carotid artery mean IMT and plasma lycopene in women but not in men. They concluded that the study provided limited support for the hypothesis that increased dietary intake of vitamin E and increased plasma lycopene may decrease the risk of atherosclerosis but they found no support for the widespread concept that supplemental antioxidant vitamins will protect against the development of atherosclerotic CAD.

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

It is now commonly accepted that oxidation of low-density lipoprotein (LDL) is important in the development of early atherosclerosis because oxidized LDL possesses a number of biological properties that may promote atherogenesis.[1,2] Animal studies have long suggested that administration of antioxidants may inhibit lipid oxidation and reduce the development of atherosclerosis.[3,4] Despite these encouraging laboratory findings, the many epidemiological studies that have investigated the relationship between antioxidant vitamins and the occurrence of vascular disease have yielded results that often were in conflict with randomized clinical trial findings.[5]

McQuillan et al's study of a large number of subjects with an equal gender ratio and broad age range provided no support for the long-held hypothesis that higher dietary consumption of the antioxidant vitamin E may reduce or prevent the development of early atherosclerosis. A number of epidemiologic studies are currently ongoing and hopefully will more clearly elucidate whether combinations of antioxidants and/or longer-term use of these agents in various populations will prevent early atherosclerosis in the normal population or even in the population of those individuals who are more susceptible to developing early vascular disease however, thus far, there certainly is no clear evidence that antioxidants provided by dietary intake or by the addition of oral agents in the form of vitamin supplements can reduce the risk of developing atherosclerosis. Until the results of these epidemiologic studies have been reported, physicians should focus their efforts on proven methods (ie, cigarette smoking cessation, exercise, lipid control, blood pressure lowering, counseling patients on avoidance of stress, weight reduction, etc.) and drug therapy (ie, aspirin, statins, beta blockers, angiotensin-converting enzyme inhibitors, etc.) for preventing symptomatic CAD and/or stroke and should not emphasize the alleged benefits of vitamin supplements or other alternative medicines until they have been clinically proven by well mounted, randomized studies. ■

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Is CT Necessary Before LP in Suspected Meningitis?

ABSTRACT & COMMENTARY

Synopsis: *This prospective emergency department study identified clinical criteria that have a 97% predictive value for a normal head CT in patients that could safely undergo LP without a CT scan.*

Source: Hasbun R, et al. *N Engl J Med.* 2001;345:1727-1733.

In this study, Hasbun and colleagues prospectively selected 11 elements of the Modified National Institutes of Health (NIH) Stroke Scale and tested how well they predict which suspected meningitis patients will have normal computed tomography (CT) of the head. The criteria tested were absence of: age older than 60, history of immunocompromise, history of central nervous system disease, seizure within 1 week, an abnormal level of consciousness, inability to answer 2 consecutive questions correctly, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language. At the Yale New Haven Emergency Department, 301 patients were enrolled sequentially from 1995-1999. Two hundred thirty-five (78%) underwent CT before lumbar puncture (LP). Of these, 189 (76%) had normal head CT. Ninety-six (40%) of these patients had none of the abnormal clinical findings listed, and of these 93 (97%) had normal head CT. The 3 patients with normal clinical findings but abnormal CT underwent LP without brainstem herniation. Among the 56 (24%) patients with abnormal clinical findings and abnormal CT, 4 had findings that caused clinicians to avoid LP and 2 of these patients eventually died with brain herniation without LP. Had these 11 clinical findings been used as criteria to not order CT prior to LP, 40% fewer scans would have been ordered without apparent harm. Hasbun et al also found that patients that had LP without first having CT had: 1) a shorter time from admission to LP, 3.0 hours vs. 5.3 hours ($P \leq 0.001$); and 2) a trend toward shorter time to antibiotic therapy, 2.9 hours vs. 3.8 hours ($P = 0.09$).

■ **COMMENT BY MARK POTTER, MD**

Bacterial meningitis is a medical emergency that requires collection of cerebrospinal fluid for optimal diagnosis and treatment. Since the 1950s, however, fatal brain stem herniation has been recognized as a rare complication of LP. Elevated intracranial pressure, especially in the setting of unilateral brain lesions,

inflammatory lesions (eg, toxoplasmosis, subdural empyema, brain abscess), intracranial hemorrhage, cerebral edema, sagittal sinus thrombosis, or central vein thrombosis increases the risk of herniation. CT scanning can identify many of these risk factors and is commonly ordered prior to LP. In this study, 44% of physicians surveyed cited the standard of care or fear of litigation as their reason for ordering the CT prior to LP. Concerns persist, however, about negative effects of routine CT scanning before LP. Concerns about delays in antibiotic treatment have been somewhat mitigated by the widely accepted practice of starting empiric antibiotic therapy prior to LP if LP is to be delayed for any reason. The exact effect of antibiotics before LP on the diagnostic use of cerebrospinal fluid cultures continues to be debated. The extra costs of scanning and prolonged ED time are also concerns. No broad consensus guideline currently exists to aid clinicians in determining when CT is needed prior to LP. This article provides some support to those seeking a clinical basis for more selective use of CT scanning in cases of suspected meningitis, but further validation in other settings and with larger cohorts will be needed to establish a clear evidence-based standard in this area. ■

Dr. Potter is Assistant Professor of Family Medicine, Loyola University Medical School, Chicago, Ill.

Pharmacology Update

Paroxetine Controlled Release (Paxil CR)—New Dosage Form for Panic Disorder

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

Recently the FDA approved paroxetine controlled-release (CR) tablets for the treatment of panic disorder. It joins the immediate-release (IR) form of paroxetine and sertraline as the selective serotonin reuptake inhibitors (SSRIs) with this indication.

Indications

Paroxetine CR tablets are indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. It is also indicated for the treatment of major depression, obsessive compulsive disorder, general anxiety disorder, social anxiety disorder, and post-traumatic stress disorder.[1]

Dosage

The recommended starting dose for panic disorder is 12.5 mg per day. The dose may be increased at 12.5 mg increments no sooner than 1 week after initiating therapy. The dose range is 12.5 mg to 75 mg per day. In clinical trials, the mean dose was 50 mg per day. The tablet should not be chewed or crushed and may be taken without regard to meals.[1]

CR paroxetine is available as 12.5-mg, 25-mg, and 37.5-mg tablets.

Potential Advantages

The incidence of nausea or vomiting may be initially less with the CR formulation compared to the immediate release (IR) formulation. In a randomized, placebo-controlled, 3-day study (n = 120), the proportion of patients reporting nausea and/or vomiting for CR 30 mg, IR 30 mg, and placebo were 40%, 59%, and 13%, respectively.[2] However, whether this is maintained over time is not known as patients tend to adapt to this side effect with continued use.[1] Paroxetine is the only SSRI currently approved for all 5 anxiety disorders. It is generally well tolerated and has a low potential for causing jitterness.[3] SSRIs have generally been considered the treatment of choice in patients who never had pharmacotherapy.[4,5] While this appears to be a class effect, they do differ in side effects and potential for drug interactions.

Potential Disadvantages

Paroxetine inhibits cytochrome P450 isoenzyme 2D6 and drugs that are metabolized by this isoenzyme must be co-administered with caution. Citalopram and sertraline are options if interaction with 2D9 is problematic.

Sexual dysfunction is a side effect of paroxetine. The most common manefestations are ejaculatory disturbance (27% vs 3% for placebo), impotence (10% vs 1%), decreased libido (8% vs 2%), and orgasmic disturbance (7% vs 1%).[1] Based on a survey questionnaire of 1022 antidepressant patients, the incidence of reported sexual dysfunction was 71% (147/208) for paroxetine. This was higher than that reported for fluoxetine 58% (161/279) and sertraline 63% (100/159).[6] Paroxetine is more sedating than sertraline or fluoxetine. Withdrawal symptoms (eg, dizziness, light-headedness, nausea, vomiting, flu-like symptoms, sensory, and sleep disturbance) upon abrupt or brief discontinuation appeared to be more likely with paroxetine than fluoxetine.[7,8] Gradual

tapering of the dose is recommended.[1]

Comments

CR paroxetine is formulated in a degradable polymeric matrix (Geometrix). It is designed to control the release of the drug over a 4-5 hour period. An enteric coat also delays the release until the table has entered the small intestine. The peak plasma level is achieved in 6-10 hours compared to about 5 hours for the IR form. The mean peak level is about one half of that of the IR form (30 ng/mL to 60 ng/mL). The elimination half-life is not altered by the delivery system. It is not clear if the CR formulation significantly alters the pharmacodynamics of paroxetine. The effectiveness in treating panic disorder was shown in 2 out of 3 10-week, placebo-controlled studies with the CR formulation.[1] The end points were proportion of patients free of full panic attacks, change from baseline in the median number of full attacks, and change from baseline in the median Clinical Global Impression Severity Score. Long-term maintenance (3 months) efficacy has been shown only with the IR formulation.[1]

Clinical Implications

It is estimated that 1.7% of the US adult population have panic disorder in any given year.[4] It primarily affects women and the incidence declines with age with the highest between 18-29 years. It tends to closely mimic medical disorders and often results in high use of health care resources and diagnostic procedures.[4] Panic disorder is characterized by a discrete period of intense fear or discomfort and 4 or more of the following symptoms that develop abruptly and reach a climax within 10 minutes: palpitations, sweating, trembling or shaking, sensation of shortness of breath or smothering, feeling of choking, chest pain or discomfort, nausea or abdominal distress, feeling of dizzy, unsteady, lightheaded, or faint, derealization or depersonalization, fear of losing control, fear of dying, paresthesias, or chills or hot flashes.[9] Pharmacologic management includes antidepressants and benzodiazepines. SSRIs are generally considered the initial treatment of choice. The specific agent should be tailored to the patient's panic symptom profile, comorbid conditions, and potential drug interactions. The regimen may need to be adjusted due to the patient's tolerance to the drug. CR paroxetine offers another formulation of an effective SSRI for the treatment of panic disorder. It is not clear if the CR formulation offers any significant advantage over the IR counterpart. ■

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CME Questions

22. Which of the following is true about blood pressure control and cardiovascular mortality?

a. Pulse pressure has no predictive value.
b. Control of systolic blood pressure is more predictive than is control of diastolic blood pressure.
c. Control of diastolic blood pressure is more predictive than is control of systolic blood pressure.
d. Systolic blood pressure has no predictive value.
e. Overall blood pressure has no predictive value.

23. Which group of OC users is more likely to have an acute MI?

a. Women who smoke
b. Women who are hypertensive
c. Women who are hypercholesterolemic
d. Women who carry the Factor V (Leiden) mutation
e. Women who are diabetic

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By Louis Kuritzky, MD

Treatment of Postherpetic Neuralgia

BEST MANAGEMENT OF POSTHERPETIC neuralgia (PHN) remains problematic, since a variety of reports suggest modest favorable effects of a diversity of interventions, with little confirmation of relative efficacy through head-to-head comparative trials. This systematic literature review included 27 randomized controlled trials felt to be methodologically sound to assess outcomes of pain and quality of life as impacted by topical (eg, lidocaine patch, capsaicin cream), oral (eg, amitriptyline, gabapentin, opioid analgesia), and other (eg, acupuncture, TENS) therapies.

Literature analysis indicated that tricyclic antidepressants (TCA) provide the best evidence for efficacy, though conclusions are limited by the short duration of trials (none > 8 weeks). Topical capsaicin, gabapentin, and opioid analgesia were also found effective. For refractory patients, methylprednisolone and bupivacaine sympathetic blocks merit consideration. Tools for which insufficient evidence to establish efficacy was found include lidocaine patch, benzydamine cream, tramadol, vincristine, and iontophoresis. Treatments deemed unlikely to be of benefit included benzodiazepines, dextromethorphan, acyclovir, and acupuncture.

Among the demonstrated effective agents, side effect profile, cost, and ease of administration ultimately determine which agent will be preferred for an individual patient. ■

Alper BS, et al. J Fam Pract. 2002;51: 121-128.

Plasma Homocysteine as a Risk Factor for Dementia and Alzheimer's Disease

ELEVATED HOMOCYSTEINE (HCYS) levels have been correlated with vascular toxicity, in particular, coronary heart disease. Conflicting reports on the relationship between HCYS and cognitive function have left the issue unresolved. Data from the Framingham Study, which details the relationship between dementia (DEM), Alzheimer's disease (ALZ) and HCYS, is presented in this study by Seshadri and colleagues.

The population studied (n = 1092) had undergone measurement of HCYS in 1986-1990, and almost all of them (86%) had had measurements obtained in the 1979-1982 time period also. Only subjects who were free of dementia at inception of the trial were included.

Over 8 years' observation, 111 subjects developed dementia (83 = ALZ); for every 5 mcmol/L increase in HCYS, the risk of ALZ increased 40%. This progressive increase in risk was not altered by adjustment for gender or age. Interestingly, since it is well known that supplementation with folate, B12, and pyridoxine may have a favorable effect upon HCYS, adjustment for plasma levels of these vitamins did not alter the relationship between HCYS and subsequent development of DEM/ALZ. It remains to be shown by interventional trials whether reductions in HCYS can translate into reduced risk for dementia. ■

Seshadri S, et al. N Engl J Med. 2002; 346:476-483.

Rapid Suppression of Alcohol Withdrawal Syndrome by Baclofen

FOR PERSONS WITH CHRONIC ALCOhol abuse habits, alcohol withdrawal is both psychologically and physically difficult, and not without risk. The distressing symptoms of withdrawal often begin 6-24 hours after initiation of abstinence, and animal studies have suggested that baclofen suppresses alcohol withdrawal syndrome symptoms. Since baclofen has also been shown to favorably effect alcohol craving and intake in persons suffering alcohol dependency, a trial to assess its use in severe alcohol withdrawal syndrome was undertaken.

Addolorato and colleagues studied 5 patients who scored higher than 20 on the Clinical Institute Withdrawal Assessment for Alcohol scale, indicative of severe alcohol withdrawal syndrome. Subjects received 10 mg baclofen orally initially, and then 10 mg orally every 8 hours for 30 days, with measurement of the Withdrawal Assessment for Alcohol scale daily for 1 week, and then weekly for the remaining 3 weeks of the treatment course.

All 5 of the patients reported rapid (within 2 hours) alcohol withdrawal symptom resolution after administration of 10 mg baclofen. Similarly, all patients were able to remain abstinent and asymptomatic using baclofen 10 mg q.8.h. The remarkably favorable outcome of this small study suggests need for a larger scale trial of this method. ■

Addolorato G, et al. Am J Med. 2002; 112:226-229.

In Future Issues:

Adding Insulin Early to Sulfonylurea Therapy is Beneficial
Out on the Border, Walking the Line