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INSIDE

New ED Drug Green-Lighted for Phase III Trials

By William T. Elliott, MD, FACP

Bayer's new erectile dysfunction (ed) drug vardenafil is entering phase III trials after European data suggest that it is effective in up to 80% of men regardless of the severity or cause of ED. The data were reported at the annual meeting of the European Association of Urology. The drug is a phosphodiesterase-5 inhibitor like **sildenafil** (Viagra), but it may be more specific for the enzyme than sildenafil, possibly resulting in fewer side effects. **Bayer** is projecting the results of this phase III testing by the end of the year, with a 2002 product launch projected.

PPI Update

The FDA has approved the first intravenous **proton pump inhibitor** (PPI). Wyeth's **pantoprozole** (Protonix IV) was approved for short-term treatment of **gastroesophageal reflux disease** in patients who are unable to take oral medications. The IV dose is the same as oral pantoprozole at 40 mg/d. This approval, however, comes at a time when the use of acid-suppressing therapy and prophylaxis of stress ulcers in the hospital is being scrutinized. A recent meta-analysis looked at the use of IV ranitidine and oral sulcrafate in this role. **Ranitidine** was no better than placebo in preventing ulcers or GI complications, and when compared to sulcrafate, ranitidine was associated with a higher rate of **nosocomial pneumonia** (*BMJ.* 2000;321:1103). The results of this article and others are forcing intensivists to re-evaluate recommendations on the prevention of stress ulcers.

Alternative Medicine

As **alternative therapies** are objectively evaluated, some are shown to be effective, such as **glucosamine** (*Lancet.* 2001;251:251-256), and some are shown to be ineffectual. A recent study from Vanderbilt suggests that **St. John's wort** may fall in the latter category. Two hundred patients with **major depression** were randomized to 8 weeks of St. John's wort or placebo. The active drug was started at 900 mg/d and increased to 1200 mg/d if there was inadequate response. Depression scores improved slightly in both groups, but there was no significant difference between the two. The active drug group did report more headaches. Shelton and colleagues conclude that there is no evidence that St. John's wort is effective in treating major depression (*JAMA.* 2001;285:1978-1986).

More Statin Developments

Statins protect against **heart attacks**, protect against **stroke**, and help prevent **type 2 diabetes**, but do they really reverse **osteoporosis**? Maybe not according to British researchers who looked at the records of nearly 82,000 patients who suffered fractures, and compared them to the records of 82,000 matched controls. The adjusted odds ratio for fracture among statin users was 1.01 compared to controls. Neither long-term use nor higher doses of statins made a difference (*JAMA*. 2001;285:1850-1855). These data contradict the results of previous studies that suggested that the drugs may build bone density (*JAMA.* 2000;283:3205-3216, *Lancet.* 2000;355:2185-2188).

There may be a new role for statins in the setting of **acute coronary syndromes** such as **unstable angina** or **acute myocardial infarction**. Two recent studies show that statins, when used before or at the time of hospital discharge, reduce subsequent events. One study pooled data from the GUSTO IIb and PURSUIT trials comparing more than 3600 patients with coronary events who were discharged on a statin with more than 17,000 patients who were not discharged on one of the lipid lowering drugs. Both 1-month and 6-month mortality were cut in half in the statin group (*Lancet*. 2001;357:1063-1068). **Atorvastatin** (Lipitor) was used in a second study of more than 3000 patients with unstable angina or non-Q-wave MI. The patients, who had an average LDL cholesterol of 124 mg/dL, were randomized to atorvastatin 80 mg/d or placebo. The duration of the study was short, only 16 weeks, but during that time, end points of MI, recurrent angina, cardiac arrest, or death were less common in the treatment group (absolute reduction 14.8% treatment vs placebo, relative reduction of 17.4%). The main benefit was reduction of recurrent symptomatic ischemia requiring rehospitalization. Although the benefit was modest, there seemed to be no risk and few adverse effects from the medication (*JAMA.* 2001;285:1711-1718).

Alosetron Could Make Limited Return

Glaxo is working with the FDA to allow limited use of **alosetron** (Lotronex), its drug for women with **irritable bowel syndrome**. The drug was pulled from the market less than 6 months ago because of cases of ischemic colitis and several deaths associated with the use of the drug. Some of the pressure to reintroduce the drug is coming from patient groups who benefited from the drug. Public Citizen, a consumer advocacy group, is urging the FDA to uphold the ban on alosetron citing evidence that there may have been even more adverse effects than initially reported.

MMR Vaccine and Autism

There is no link between the **measles, mumps, rubella** (MMR) vaccine and **autism** according to the findings of a committee commissioned by the Institute of Health. The report, released in April, reviewed all available data and even commissioned its own epidemiologic study. The 15-member expert panel was composed of epidemiologists, pediatricians, biostatisticians, and public health experts picked, in part, because of their lack of ties to the vaccine industry. The concern in this country was heightened in 1998 by a report in *Lancet* suggesting that the vaccine may be associated with autism-like symptoms. But the current panel exonerates the vaccine, saying it is as "safe as a vaccine can get." ■

Once-a-Week Fluoxetine, 'Prozac Weekly'

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

With the pending patent expiration of fluoxetine (Prozac), Eli Lilly is introducing another version of their blockbuster selective serotonin reuptake inhibitor (SSRI). Following the introduction of fluoxetine as Sarafem for premenstrual dysphoric disorder, Lilly has received FDA approval to market a once-weekly formulation of the drug for the treatment of depression. This takes advantage of the long elimination half-lives of the fluoxetine and its active metabolite, norfluoxetine, along with formulation of the drug in enteric-coated pellets. The product is marketed as Prozac Weekly.

Indications

Fluoxetine is indicated for maintaining an antidepressant response after initial acute treatment with fluoxetine 20 mg.[1,2]

Dosage

Fluoxetine 90 mg is dosed once-weekly. Weekly dosing should be initiated 7 days after the last daily dose of fluoxetine 20 mg. Fluoxetine Weekly is available as a 90-mg capsule.

Potential Advantages

Once-weekly dosing may improve compliance and may also enhance psychological well being.[1] Findings from a study by Lilly suggest that compliance with once-weekly dosing was higher compared to daily dosing, 85.9% vs. 79.4%.[3]

Potential Disadvantages

It is not clear if once-weekly administered fluoxetine provides the same degree of protection from relapse as once-daily fluoxetine.[2] Average trough plasma concentrations were 76% lower for fluoxetine and 47% lower for the active metabolite, norfluoxetine.[2] A weekly dosing regimen is an uncommon regimen, and some patients may have difficulty remembering their doses.

The effect of variation in GI transit time (eg, diarrhea) on the pharmacokinetics of fluoxetine-weekly is not known. Fluoxetine-weekly has not been studied for other conditions such as obsessive compulsive disorders, bulimia nervosa, or premenstrual dysphoric disorder.

Comments

The long elimination half-lives of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (about 9 days) are conducive to less frequent dosing. The efficacy of a weekly regimen is supported primarily by a multicenter, placebo-controlled, double-blind, randomized study.[1]

Patients with DSM-IV criteria for nonpsychotic major depression and who had a modified 17-item Hamilton Rating Scale for Depression (HAM-D-17) of 18 or greater and a Clinical Global Impression-Severity of Illness scale (CGI-S) score of 4 or greater were treated with fluoxetine 20 mg for 13 weeks. A total of 501 responders (HAM-D-17 of 9 or less and CGI-S of 2 or less) were then randomized to fluoxetine 90 mg weekly, fluoxetine 20 mg, or placebo for 25 weeks. The primary end points were the percent of patients that relapsed and time to relapse. Relapse was defined as meeting criteria for major depression and an increase in CGI-S score of 2 or more relative to the rating before randomization. The percentages of relapse were 26% for fluoxetine 20 mg, 37% for fluoxetine-weekly, and 50% for placebo. While there was no statistical difference between fluoxetine regimens, daily dosing was numerically higher.

The times to relapse were 105 days, 109 days, and 86 days for fluoxetine 90 mg, 20 mg, and placebo, respectively. Nervousness and impaired concentration or thought process were the most frequent side effects for the 90-mg dose compared to the 20-mg dose, 13.7% vs. 6.3% and 8.9% vs. 1.6%, respectively. However, these side effects were similar to the frequencies seen with placebo. Prozac Weekly is priced about 5% less than Prozac daily.

Clinical Implications

Fluoxetine 90 mg weekly may be considered for maintenance therapy for patients who have responded to daily administered fluoxetine. The effectiveness may be less than that of a daily regimen in preventing relapse. If a satisfactory response is not achieved, returning to a daily regimen should be considered. ■

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Galantamine: A New Agent for the Treatment of AD

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

The fda has approved the fourth acetylcholineasterase (AchE) inhibitor for the treatment of Alzheimer's disease (AD). Galantamine, a reversible competitive inhibitor of AchE, is an alkaloid that was originally extracted from bulbs of the daffodil. It has been in use in several other countries for decades.[1] Galantamine is marketed by Janssen Pharmaceutica as Reminyl.

Indications

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

Dosage

The recommended starting dose is 4 mg twice daily for a minimum of 4 weeks. If the dose is tolerated, the dose should be increased to 8 mg twice daily. After a minimum of 4 weeks, an increase to 12 mg twice daily should be attempted.[2] Doses should be administered with morning and evening meals to reduce gastrointestinal side effects. In the clinical trials, the dose of 24 mg was not statistically superior to 16 mg, but some patients may gain additional benefit. The 32-mg dose is less tolerated and does not appear to offer additional benefit. In patients

with moderate hepatic or renal impairment, the dose should not exceed 16 mg/d. The use of galantamine is not recommended in patients with severe hepatic or renal impairment.[2]

Galantamine is supplied as 4-mg, 8-mg, and 12-mg tablets.

Potential Advantages

Galantamine appears to have a low potential for interacting with the major cytochrome P450 isoenzymes.[2] In addition to inhibition of AchE, galantamine interacts with the nicotinic acetylcholine receptors. This action is believed to enhance the action of acetylcholine on the receptors resulting in the release of acetylcholine and other neurotransmitters such as glutamate.[3,4] This "additional" mechanism has yet to be demonstrated clinically. The FDA has not allowed a claim of dual mechanism of action in the product labeling.

Potential Disadvantages

Galantamine requires at least 8 weeks to reach the target dose of 24 mg/d. Most common side effects compared to placebo are gastrointestinal, nausea (24% vs 9%), and vomiting (13% vs 4%).[2]

Paroxetine increases the oral bioavailability of galantamine by 40%.[2]

Galantamine requires twice-daily dosing.

Comments

The efficacy of galantamine in mild-to-moderate Alzheimer's disease was reported in 3 large 5- or 6-month studies, of which 2 were from the United States and 1 was international.[5-7] There were 653 subjects in the international trial, 978 in the 5-month US study, and 636 in the 6-month US study. Diagnosis of probable AD was based on the National Institute of Neurologic and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA), a score of 10 or more and 24 or less on the Mini Mental State Examination score (MMSE), and a score of 12 or more on the standard 11-item cognitive subscale of the Alzheimer's Assessment Scale (ADAS-cog). The primary efficacy measures were the ADAS-cog and the Clinician's Interview Based Impression of Change plus Caregiver Input (CIBIC-plus). Patients were escalated to a maintenance dose of 8-32 mg/d. Measures were analyzed on an intent-to-treat as well as on an observed case basis. Observed cases are those with post-baseline data using last-observation-carried-forward (LOCF). Galantamine showed a difference in ADAS-cog between placebo in intent-to-treat analysis of 3.1 for 16 mg/d, 0.1-3.1 for 24 mg/d, and 3.2-3.4 for the 32 mg/d. On the observed case basis, the results were 3.3, 3.2-3.9, and 3.8-4.1, respectively. Roughly 1/3 of patients achieved clinically meaningful improvement of 4 units or greater compared to 15-20% on placebo. About 2/3 (64-70%) of subjects showed improvement in the CIBIC-plus compared to about half (47-55%) on placebo.

Galantamine has been reported to reduce the time caregivers spent assisting patients with activity of daily living of 15-38 min/d compared to an increase of 23 min in the placebo group.[3,8]

Clinical Implications

Currently, there are no direct comparisons among the available AchE inhibitors—tacrine, donepezil, rivastigmine, and galantamine—however, it appears that their effects on ADAS-cog are similar in magnitude. Their potential secondary pharmacologic actions may differ.

Rivastigmine inhibits butrylcholinesterase while galantamine is a modulator of the nicotinic receptors. The importance of these secondary mechanisms have not been established. Until there is more comparative information, donepezil may be preferred because of its convenient once-daily dosing and it generally does not require dose titration. Rivastigmine, donepezil, and galantamine are priced similarily. ■

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Does Pravastatin Prevent Stroke?

Source: *Byington RP, et al. Circulation. 2001;103:387-392.*

Strokes, which are the second leading cause of death in the Americas and Europe, occur in 600,000 patients each year and are the leading cause of disability and increased health care costs in the United States resulting in 160,000 deaths.[1] Whereas

numerous studies have demonstrated that the risk of coronary heart disease events is reduced by lipid-lowering therapy,[2-6] the effects of lipid-lowering on stroke events have not been well established even though studies with older lipid-lowering agents have suggested that modest reduction in cholesterol did not reduce stroke.[7,8] More recently, the proven efficacy of the HMG-CoA reductase inhibitors (or statin drugs) on the ravages of coronary artery disease have heightened the expectation that these agents might also have a beneficial effect on the prevention of stroke.

The Prospective Pravastatin Pooling (PPP) Project was initiated in 1992 before 3 large, placebo-controlled, randomized trials, which included 19,768 patients with 102,559 person-years of follow-up, had been completed. The effect of pravastatin given in a dosage of 40 mg/d on stroke events was investigated, and a prospectively defined pooled analysis of these 3 large trials[4-6,9-11] was performed.[12] When the 13,173 patients from the 2 secondary prevention trials[7,8] were combined, there was a 22% reduction in total strokes and a 25% reduction in nonfatal stroke. The beneficial effect of pravastatin on total stroke incidence was observed across a wide range of patient characteristics. Pravastatin was associated with a 23% reduction in nonhemorrhagic stroke in the secondary prevention group. The West of Scotland Coronary Prevention Study, which was a primary prevention trial in hypercholesterolemic men, exhibited a similar, although somewhat smaller, reduction in total stroke incidence.

Comment by Harold L. Karpman, MD, FACC, FACP

The data presented by Byington and colleagues in the Prospective Pravastatin Pooling Project represent a carefully performed systematic overview of 3 extremely large lipid-lowering trials. The pooled results demonstrate a statistically significant reduction in total stroke and nonfatal stroke attributable to pravastatin administration. The analyses also clearly demonstrated that pravastatin was more effective than the older, nonstatin lipid-lowering therapies in reducing stroke rates. The consistent reduction in stroke rate across the trials and subgroups were particularly striking, and the drug appeared to have similar beneficial effects on patients taking aspirin and whether they were taking blood pressure-lowering medications.

It is important to recognize that stroke has many causes; therefore, in evaluating specific forms of drug therapy used for prevention, one must separate thrombotic from hemorrhagic strokes. Pravastatin appears to have strong beneficial effects in preventing atherothrombic strokes and has no effect on the prevention of hemorrhagic stroke. Since numerous papers suggest that plaque rupture is the primary pathogenic mechanism in acute thrombotic events in coronary and cerebral arteries, plaque stabilization appears to be an important process by which statins are effective in reducing the frequency of thrombotic events in these areas. Therefore, the nonlipid effects of statin drugs may be more important in the prevention of cerebrovascular disease than are the lipid-lowering actions of the drug. Also, statins have been shown to have an anti-inflammatory effect independent of their LDL-lowering actions by virtue of their ability to reduce inflammatory markers such as C-reactive protein, and this effect may result in improved endothelial function thereby decreasing the incidence of acute coronary events.

From a clinical point of view, the PPP Project results provide strong evidence supporting the view that patients with a prior history of myocardial infarction should be treated with statin drugs—not only to prevent recurrent myocardial infarctions but also possibly to reduce the incidence of stroke event rates. Since stroke is a devastating event in the lives of patients and their families, clinicians should be able to use the results of the PPP Project to generate greater patient acceptance of prolonged statin therapy. Although the principle use of these drugs will largely remain in the prevention of coronary artery heart disease, the evidence of stroke benefit with the use of statin drugs demonstrated by the PPP Project is an important contribution for both clinicians and patients. As we enter an era in which we may be using statin therapy to treat and prevent all cerebrovascular and peripheral arterial thrombotic events and, in fact, even for the treatment of occult atherosclerosis in all arterial systems, we thereby will be reducing the incidence of acute coronary and cerebrovascular events. ■

Dr. Karpman is Clinical Professor of Medicine, UCLA School of Medicine, Los Angeles, Calif.

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How Far to Lower LDL Cholesterol: Important New Data

Sources: *Smilde TJ, et al. Lancet. 2001;367:577-581; Durrington PL. Lancet. 2001;367:574.*

Asap, the effect of aggressive vs. conventional Lipid Lowering on Atherosclerosis Progression in Familial Hypercholesterolaemia, is a prospective randomized trial in individuals with familial hypercholesterolemia (FH) treated with aggressive vs. less aggressive statin therapy for 2 years. The primary end point was a change in carotid intima medial thickness (IMT), with a number of secondary end points at 24 months. Eligible patients were untreated (1/3) or were on therapy but still had an LDL-C greater than 175 mg/dL. After a run-in period of 2 months, with baseline measurements of IMT and a variety of lipoproteins, 325 patients (mean age, 48) were randomized to 80 mg of atorvastatin or 40 mg of simvastatin. One-third had overt cardiovascular disease, and one-third were smokers. A resin was added to therapy if total cholesterol remained greater than 320 mg/dL. All individuals were recommended to be on a standard low-fat diet. B-mode ultrasound was used, with measurements of the distal common corotid artery, carotid bifurcation, and the proximal internal carotid artery; IMT was determined for both anterior and posterior walls of the common carotid and bifurcation.

Results: 14% of patients did not complete the protocol for a variety of reasons. There was a low cardiovascular event rate; muscle aches and mild abdominal complaints were common in both groups (there was no placebo arm). Baseline TC was 400 mg/dL, and LDL-C was approximately 320 mg/dL. Lipid levels dropped dramatically. Atorvastatin (A) lowered LDL-C by 50% (P = .0001), with a reduction TC of 42%, TG 29%, and an increase in HDL of 13%. Simvastatin (S) lowered TC by 34%, LDL-C by 41%, TG by 18%, with a comparable increase in HDL-C. There was a marked change in the LDL/HDL ratios in both groups. Twenty-seven percent of A individuals had a fall in LDL-C below 120 mg/dL, but only 7% of the S patients achieved these levels. Lp(a) levels decreased by 15% in both groups. IMT changes were notable. Overall IMT was reduced in the A group but increased in the S group, with highly significant P-values. Thus, regression of carotid IMT was noted in 66% of A patients and 42% of S patients. Overall changes in IMT were correlated with baseline IMT (thicker vessels demonstrated greater changes) and with the percentage of cholesterol reduction. Changes in HDL and Lp(a) did not correlate with changes in IMT. Smilde and associates conclude that aggressive LDL cholesterol lowering of at least 45-50% is warranted in patients with FH to modify IMT progression and produce regression. While HDL did not seem to relate to IMT, triglycerides did; they speculate that triglyceride rich LDL and small dense LDL particles may be favorably altered by aggressive statin therapy and play a role in favorable changes in IMT. They point out that their data are consistent with the Post CABG Trial, which compared a modest vs. high dose of lovastatin in patients with prior bypass surgery, and demonstrated a more favorable effect on slowing progression of saphenous graft disease in the high-dose lovastatin subjects, who achieved a final LDL-C of less than 90 mg/dL. They emphasize that the A subjects in ASAP not only had limited progression but actually reversed atherosclerosis, as assessed by IMT; the data are concordant and correlate LDL-C reduction to favorable changes in IMT. They point out that a yearly IMT progression rate of 0.03 mm or greater increases the risk of future events, based on data in the literature. The 0.07 mm difference in IMT between A and S at 2 years suggests that less effective LDL-C lowering did not achieve sufficiently favorable results in this high-risk subject. They concluded that IMT is an adequate surrogate end point for vascular disease, although there are significant limitations using this marker; "aggressive lipid lowering is indicated, beneficial, and safe in patients with FH."

Comment by Jonathan Abrams, MD

The data in this study are striking, suggesting for the first time that a large number of patients with FH can have their vascular disease stabilized and potentially even regressed. The comparison of 80 mg of atorvastatin to 40 mg of simvastatin is unfair, in one sense, as it is no surprise that greater LDL-C reductions can be achieved with high-dose atorvastatin. As to what is the best end point for lowering LDL cholesterol, the arguments remain: should it be a percentage reduction, achievement of a target level, or simply reaching a specific level, such as 125 mg/dL, as the CARE

investigators recommend. This study clearly supports that greater lowering is more favorable, and the fact that IMT actually regressed over 2 years, associated with a 50% reduction in baseline LDL-C, is compatible with much other data. Thus, lower is better, certainly in FH patients, and probably in other individuals at high risk. These would include an elevated LDL-C in individuals who have established vascular disease and/or multiple other CAD risk factors. The absence of a placebo arm in this trial makes it difficult to know whether simvastatin slowed progression; this is likely but is unproven. In that the mean baseline total cholesterol in this FH cohort was 400 mg/dL, and the LDL-C was approximately 320 mg/dL, there is little to dispute over a target of LDL reduction of 50% or even greater.

The role of carotid IMT as a marker for vascular disease and atherosclerosis seems reasonably well founded. Multiple studies have or are using this technique. Meticulous attention to detail is necessary. The slope of change is important, and clearly a negative slope, as seen with the high dose atorvastatin group, is an exciting finding. I am unaware of other regression trials that show that the majority of individuals treated with lipid lowering actually regress as opposed to having stabilized disease and slowed progression. It is reasonable to extrapolate from the FH patients in this trial to high-risk individuals in general, from either a primary or secondary prevention perspective. In patients with established vascular disease, LDL-C should (and can) be brought to below 100 mg/dL and probably even lower. The actual levels achieved in the FH patients are much higher, of course. One can extrapolate from the 2-year differences in LDL and IMT between the simvastatin and atorvastatin groups that reducing high levels of total and LDL cholesterol to levels approaching "normal" is most beneficial for patients with high cardiovascular risk. ■

Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.

Caspofungin—A Novel Antifungal Agent

By Stan Deresinski, MD, FACP

Caspofungin (cancidas), the first of a new class of antifungal agents, received approval by the FDA on January 26, 2001. Caspofungin is an echinocandin, a semisynthetic derivative of pneumocandin B0, which is a fermentation product of *Glarea lozoyensis*. It is a large (MW 1213 daltons), water soluble lipopeptide that, like other echinocandins, competitively inhibits the synthesis of b-(1,3)-D-glucan, a critical structural component of most fungal cell walls.[1]

Among fungi frequently encountered in the clinic, caspofungin has in vitro and in vivo activity against *Aspergillus* and *Candida* species and is also active in animal models of *Pneumocystis carinii* infection. Since its mechanism of action differs from those of the polyenes and the azoles, caspofungin retains activity against many fungal organisms resistant to these 2 classes of agents. It has activity against all *Candida* spp., including *C krusei*, is fungicidal against *Candida* spp. in a concentration-dependent manner, and has sterilizing abilities in a murine model of pyelonephritis. When combined in vitro with amphotericin B against either *C albicans*, *A fumigatus*, *Fusarium* spp., or *Cryptococcus neoformans*, either synergy or indifference is observed; antagonism has not been described. Antagonism was also not observed in experimental infection models of candidiasis (caspofungin plus either amphotericin B or fluconazole) or aspergillosis (caspofungin plus amphotericin B).

The in vitro activity of caspofungin against the endemic fungi, *Coccidioides immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatiditis* is less than that against *Candida* and *Aspergillus*. One study reported limited activity in a murine model of histoplasmosis.[2] ■

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Therapeutics & Drug Briefs

Review of Predictors of Maintenance of Normotension After Withdrawal of Antihypertensive Drugs

Source: *Nelson M, et al. Am J Hypertension. 2001;14:98-105.*

A substantial minority of patients receiving antihypertensive medications remains normotensive upon cessation of treatment. Some of these individuals were treated prematurely, without adequately establishing a diagnosis of hypertension (HTN) with certainty. Others have eliminated the etiology for their elevat-

ed blood pressures (eg, obesity or alcohol) but continue on unnecessary medication. All the reasons for restoration of normotension in some hypertensive patients are unknown. Clinicians and their patients would benefit from knowing which predictors are associated with sustained normotension after medication withdrawal. To that end, the authors reviewed articles that examined withdrawal of antihypertensive medications in persons who subsequently remained normotensive for at least 12 months.

Approximately 42% of patients in whom medication was withdrawn remained normotensive for at least 12 months. Patients with lower pretreatment or on-treatment BP, those with good control on fewer agents or lower doses, and those who used weight reduction and salt restriction at the time of medication withdrawal predictably experienced greater likelihood of remaining normotensive upon cessation of antihypertensive therapy. Patients with mild-to-moderate hypertension, especially those with favorable predictors, should be periodically considered for a trial of treatment cessation. ■

ERT and Ovarian Cancer

Source: *Rodriguez C, et al. JAMA. 2001;285:1460-1465.*

The preponderance of epidemiologic data associates both endometrial and breast cancer with postmenopausal estrogen replacement therapy (ERT). The relationship of ovarian cancer to ERT is less clear. Recent case-control studies have suggested an increased risk with ERT, especially of long duration. Rodriguez and colleagues investigated the association between ERT and ovarian cancer mortality in a large population of female participants in the Cancer Prevention Study II (n = 676,526). Data were accrued over 14 years of observation, and include almost 1000 ovarian cancer deaths.

Even users of ERT had a slightly increased rate of ovarian cancer mortality (rate ratio = 1.23). This positive association increased in strength with duration of ERT use, so that persons using ERT for more than 10 years had an approximately 2-fold increase in relative risk. When coupled with the earlier case-control studies, this current report strengthens the concerns that ERT, especially of long duration, increases the risk of ovarian cancer mortality. Nonetheless, since total lifetime risk of ovarian cancer mortality is relatively small (< 2%), other potential favorable effects of ERT in other tissue compartments must be taken into account in the risk-benefit analysis. Additionally, the effect of concomitant progestational treatment has not been comprehensively addressed. ■

The Therapeutics & Drug Briefs were written by Louis Kuritzky, MD, Clinical Professor, University of Florida, Gainesville, Fla.

CME questions

Testing form inserted in the July 2001 issue

9. If the initial dose is tolerated, which of the following is correct regarding the next dosing schedule for galantamine?

a. After initial starting dose of 8 mg twice daily for a minimum of 6 weeks, dose should be increased to 14 mg twice daily.
b. After initial starting dose of 4 mg twice daily for a minimum of 4 weeks, dose should be increased to 8 mg twice daily.
c. After initial starting dose of 4 mg twice daily for a minimum of 2 weeks, dose should be increased to 10 mg twice daily.
d. After initial starting dose of 6 mg twice daily for a minimum of 4 weeks, dose should be increased to 12 mg twice daily.

10. Fluoxetine Weekly:

a. is marketed as Prozac Weekly.
b. is available as a 90-mg capsule.
c. may be considered for maintenance therapy for patients who have responded to daily administered fluoxetine.
d. has not been studied for other conditions such as obsessive compulsive disorders, bulimia nervosa, or premenstrual dysphoric disorder.
e. All of the above

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