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The WHI and Quality of Life

ABSTRACT & COMMENTARY

An analysis of the effect on memory, sleeping, and mental status of daily estrogen-progestin administration to postmenopausal women, based on data from the discontinued arm of the Women's Health Initiative (WHI), was summarized on the Internet site of the *New England Journal of Medicine* on March 17. The publication is scheduled for the May 8, 2003 issue of the *New England Journal of Medicine*, but the journal decided to release the results early "because of their importance." The data indicated no positive effects on emotional health, depressive symptoms, energy levels, memory, sleeping, or sexual satisfaction. There was a statistically significant benefit on sleep disturbance, physical functioning, and bodily pain; however, Hays and colleagues state that this was small and not clinically meaningful. An analysis restricted to the 574 women aged 50-54 who had moderate-to-severe vasomotor symptoms at baseline revealed a beneficial effect only on sleep disturbance (Hays J, et al. www.nejm.org. Accessed April 7, 2003).

COMMENT BY LEON SPEROFF, MD

The message sent by the authors of this WHI analysis, and repeated by the media, is that postmenopausal hormone therapy should be used only as brief treatment for severe menopausal symptoms. The experts quoted (for example, by the *New York Times*) were individuals with a track record of antihormone sentiments and statements. Deborah Grady said, "There is no place for this treatment in women who are not having hot flashes." JoAnn Manson of Harvard and the Nurses' Health Study said that the new results dispel the myth that hormone therapy improves the quality of life.

Do the editors of the *New England Journal of Medicine* really believe they are performing a service by releasing this information in this manner? The media report and seek quotes emphasizing the most negative possibility. The *New York Times* article was titled "Hormone Therapy Is Now Said to Lack Benefits." Clinicians cannot respond with knowledge and authority because the detailed results were not readily available for analysis. Of course, patients ultimately pay the price for what is, in my view, an unconscionable act on the part of this respected medical journal. Did it make me sign up for the *New York Times* web site? Yes! Does it score points for the

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INSIDE

New England Journal in its competition with other leading medical journals? Yes! Does it make clinicians angry? Yes! Does it harm patients? Yes!

Why is it possible that the reported WHI results do not apply to the majority of women for whom we prescribe hormone therapy? Remember that the participants in the WHI had an average age of 67 and were 18 years distant from their menopause. The WHI investigators like to point out that the group of women in their early 50s in the WHI presented similar findings. However, women with significant menopausal symptoms were excluded from the study to avoid an exceedingly high drop-out rate in the placebo group. Women who had been on hormone therapy (about 25% of the participants) and then underwent a 3-month "washout" period and experienced menopausal symptoms were discouraged from participation (about 12.5% of the participants reported vasomotor symptoms upon entry but were willing to be assigned to placebo, and, therefore, their symptoms were unlikely to have had a major disturbing effect). This exclusion means that only a small number of women in the WHI were close to their age of menopause (about 16.5% of the participants were less than 5 years since their menopause). The analysis of women aged 50-54 was based on about 250 women in the treated group and 225 in the placebo group. The WHI was a study of elderly women who were not representative of the population receiving hormone therapy. In addition, the inclusion and exclusion criteria of a randomized trial often produce a relatively homogenous study group. Is it possible that this group had a quality of life unlikely to be affected by hormone therapy?

There are 10 WHI publications in preparation and another 16 scheduled. Unfortunately, we face the prospect of repetitive political journalism with predictable media reporting. The burden will be great for clinicians and patients.

I believe a theme has emerged from the epidemiologic confusion of the last few years: It takes healthy tissue to allow effective responses to estrogen and to maintain health. Experimental evidence in monkeys and women indicates that as endothelial cells become involved with atherosclerosis and neurons become affected with the pathologic process of Alzheimer's, beneficial responses to estrogen diminish.[1-3] Maximal benefit, therefore, requires early onset of treatment near the time of the menopause, a principle of treatment that has not been tested by the WHI.

I do not believe the WHI results negate long-term postmenopausal hormone therapy in selected individuals. The most effective and appropriate method to help in decision-making is to identify the specific goals and objectives of the individual patient. For one patient, the goal may be protection against fractures, for another, prevention of Alzheimer's disease, and for another, relief from menopausal symptoms. Once identified, choices from the multiple available treatment options can be reviewed. This is at least an annual process, incorporating new knowledge as it appears. Approached in this fashion, the terms "short-term" and "long-term," and the imposition of time limits for therapy become meaningless. Clinician and patient together make a periodic, appropriate clinical judgment that is directed to accomplishing the individual patient's goals. ■

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A Phase II Study of Docetaxel in Paclitaxel-Resistant Ovarian and Peritoneal Carcinoma: A Gynecologic Oncology Group Study

ABSTRACT & COMMENTARY

Synopsis: *Docetaxel is active in paclitaxel-resistant ovarian and peritoneal cancer, but, in view of significant hematologic toxicity, further study is warranted to ascertain its optimal dose and schedule.*

Source: Rose PG, et al. *Gynecol Oncol*. 2003;88: 130-135.

WITHIN THE GYNECOLOGIC ONCOLOGY GROUP, Rose and colleagues conducted this phase II study of a relatively new drug, docetaxel, which is a taxane agent (related to paclitaxel [Taxol]) that is an inhibitor of microtubule depolymerization and has demonstrated activity in paclitaxel-resistant breast cancer and gynecologic cancer. Sixty patients were entered and treated with a total of 256 courses, with all 50 evaluable for toxicity and 58 evaluable for response. Responses were observed in 22.4% of patients, with 5.2% achieving complete response and 17.2% achieving partial response. The median duration of response was 2.5 months. The likelihood of observing a response did not appear to be related to the length of the prior paclitaxel-free interval or duration of prior paclitaxel infusions. The principal adverse effect of grade 4 neutropenia occurred in 75% of patients. There was 1 treatment-related death. Dose reductions were required in 36% of patients. Rose et al concluded that docetaxel is active in paclitaxel-resistant ovarian and peritoneal cancer but also indicated that, in view of significant hematologic toxicity, further study is warranted to ascertain its optimal dose and schedule.

COMMENT BY DAVID M. GERSHENSON, MD

Like paclitaxel (Taxol®), docetaxel is a taxane drug that has activity against epithelial ovarian cancer. Randomized phase III trials have demonstrated that the combination of docetaxel + carboplatin has efficacy equivalent to the combination of paclitaxel + carboplatin in patients with newly diagnosed advanced epithelial ovarian cancer. Importantly, docetaxel has considerably less associated neurotoxicity than paclitaxel but more myelotoxicity. Docetaxel is being used increasingly in the first-line setting in combination with carboplatin, and it is also being used more commonly in the recurrent setting. In general, most oncologists have preliminarily considered docetaxel and paclitaxel to be interchangeable in terms of activity. Similarly, if a patient has demonstrated tumor resistance to one of the taxane agents, it has been thought that resistance to the other taxane is likely (cross-resistance). In fact, this study demonstrates that there is not complete cross-resistance, since 22.4% of all patients with paclitaxel-resistant ovarian and peritoneal cancer who received docetaxel responded. As expected, neutropenia was the most bothersome side effect, but the starting dose of docetaxel in this study was 100 mg/m^2. Lower doses can ameliorate this toxicity. As Rose et al correctly note, the findings of this study clearly expand our armamentarium against ovarian cancer, but future studies will be required to establish the optimal dose and schedule for this interesting agent. ■

Sacrospinous Cervicocolpopexy with Uterine Preservation for Elderly Women

ABSTRACT & COMMENTARY

Synopsis: *Sacrospinous cervicocolpopexy with uterine conservation in elderly women with prolapse can be used to avoid the morbidity of hysterectomy.*

Source: Hefni M, et al. *Am J Obstet Gynecol*. 2003; 188:645-650.

PRESERVATION OF THE UTERUS USING THIS PROCEDURE has been previously described in younger women with uterovaginal prolapse.[1,2] In this nonrandomized, prospective trial conducted in the United Kingdom, 109 women with symptomatic uterine prolapse underwent either sacrospinous cervicocolpopexy (n = 61) or vaginal hysterectomy with sacrospinous colpopexy (n = 48).

Patients were allocated to the uterine-conserving procedure if the patient expressed a desire to retain the uterus and also had no evidence of postmenopausal bleeding, abnormal Pap smear, or other uterine disease.

The group in which the uterus was preserved in each

patient had less blood loss, shorter surgical times, and fewer complications. With a maximum of 34 months follow-up, the groups were similar with regard to upper vaginal or uterine support, recurrent cystocele formation, and need for repeat surgery for prolapse. Based on these data, it appears that the gynecologic surgeon need not feel compelled to perform hysterectomy in these patients.

COMMENT BY FRANK W. LING, MD

It should be noted that some of the patients in the hysterectomy group were previously reported.[3] In addition, the decision to perform a sacrospinous colpopexy at the time of the vaginal hysterectomy was made at the conclusion of the hysterectomy (ie, if the vault could be pulled to or beyond the hymen and/or a large enterocele were present). This weakens the methodology of the study, but the learning points remain.

Thorough preoperative assessment is critical since the likelihood of a need for sacrospinous fixation can be determined in the office. As with these patients, objective measurements of the various areas for prolapse should be used as should urodynamic testing.

In those patients who had uterine conservation, No. 1 polydioxanone sutures were inserted in the right sacrospinous ligament with the Miya hook. The sutures were then loaded on a No. 4 Mayo needle and passed through each side of the posterior aspect of the cervix at the level of the insertion of the uterosacral ligament. These were then passed through the vagina and either side of the midline. Pulley sutures were created to ensure good contact between cervix and sacrospinous ligament.

As elderly patients are at greater risk for surgical and postoperative complications, the potential benefits of avoiding a more morbid procedure should be considered. Other even less-invasive options such as pessary use and colpocleisis are also viable options in properly selected patients. Although the success of pessaries is variable, it is clearly the treatment of least risk. Colpocleisis is a problem for some patients as it removes the option of subsequent vaginal penetration during sexual activity. There is also the limitation that this procedure prevents access to the uterus. Of note, using the described procedure, the uterus is still accessible for uterine sampling and/or Pap smears.

Although somewhat flawed methodologically, this paper does give the gynecologic surgeon caring for the elderly patient with symptomatic prolapse another option in addressing the many needs of these patients. Contrary to what has been taught in the past, hysterectomy for these patients is not a necessity. ■

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Oral Contraceptives and Hypertension

ABSTRACT & COMMENTARY

Synopsis: *The use of oral contraceptives in women with hypertension produced higher blood pressures and poor control of blood pressure.*

Source: Lubianca JN, et al. *Contraception*. 2003;67: 19-24.

LUBIANCA AND ASSOCIATES FROM PORTO ALEGRE, Brazil, reviewed the experience of 171 women attending a clinic for the treatment of hypertension. Users of oral contraceptives had higher diastolic blood pressures (an average of 7 mm higher), and a greater prevalence of significant hypertension reflected inadequate control. There were a higher number of women with moderate-to-severe hypertension among the oral contraceptive users.

COMMENT BY LEON SPEROFF, MD

The standard of treatment for many years has been to support the use of oral contraceptives in women younger than 35 years of age with hypertension well controlled by medication, as long as they are otherwise healthy and do not smoke. Of course, the lowest dose estrogen formulations are recommended. This has been a judgment based upon the argument that careful monitoring and treatment of the blood pressure would maintain pressures below 140/90 and allow continuation of oral contraceptive usage. The problem is a lack of data in such patients.

There are important unanswered questions. How does the use of oral contraceptives influence the efficacy and stability of antihypertensive treatment? Do women with controlled hypertension who use oral contraceptives have a greater risk of cardiovascular events?

This study is limited by its cross-sectional nature, but it does suggest that oral contraceptive use has a negative effect on blood pressure control in hypertensive patients. I have heard of a case-control study, not yet published, indicting a higher risk of myocardial infarction and

stroke in women with controlled hypertension who use oral contraceptives. Therefore, there is reason for increasing concern with these patients.

Certainly, a woman with controlled hypertension who has additional medical problems or who smokes should not use oral contraceptives. At this point in time, the data are insufficient to categorically ban the use of oral contraceptives in young women with controlled hypertension who are otherwise healthy. However, very frequent and close monitoring of the blood pressure is essential. An adverse effect on the medical control, the hypertension is an urgent message to use another contraceptive method. Myocardial infarction and stroke rarely occur before the age of 35, and for this reason 35 is an accepted cutoff age limit for oral contraceptive use in women with risk factors for cardiovascular disease. ■

Women's Perceptions About Treatment Decision-Making for Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Women with advanced epithelial ovarian cancer did not describe the treatment decision-making process as shared; rather, they described an interaction that was directed by their physician.*

Source: Elit L, et al. *Gynecol Oncol*. 2003;88:89-95.

ELIT AND COLLEAGUES CONDUCTED IN-DEPTH SEMI-structured interviews with 21 patients who underwent initial surgery for stage III or IV ovarian cancer and who had received less than 2 cycles of chemotherapy. Their analysis highlighted 5 themes:

1. **Knowledge of treatment benefits and risks.**
   Women understood that the treatment had both survival and quality-of-life benefits. Women could clearly articulate the risks of chemotherapy.
2. **Readiness to make a decision.**
   When making treatment decisions, women described being overwhelmed by the effects of concurrent drugs like analgesics, the severity of the illness, unexpected diagnosis of cancer and grief, and feeling pressured into a decision.
3. **Perception of a treatment choice.**
   Most women felt that they made their treatment decision; however, most women did not perceive that they had a treatment choice. Thus, treatment decision-making is really a process of coming to terms with the disease and the recommended treatment.
4. **Physician-patient relationship.**
   All women suggest that their doctor knew the right treatment for them and they felt confident in their cancer physician.
5. **Social supports.**
   Women described supports through decision-making processes that included individuals who advocated for them, faith, and past experience with the cancer system. Hindrances to decision-making included people who were negative, the cancer label, and employers. Elit et al concluded that women with advanced epithelial ovarian cancer did not describe the treatment decision-making process as shared; rather, they described an interaction that was directed largely by the physician. These women attribute this form of decision-making to their advanced age, severity of illness, immediate ramification of treatment choices, and lack of advocacy for a different model of interaction. They further concluded that the onus is on the physician to ensure that there is an environment for shared decision-making in the event that the patient is interested in such an interaction.

COMMENT BY DAVID M. GERSHENSON, MD

This study underscores the importance of the doctor-patient relationship surrounding the initial diagnosis of advanced epithelial ovarian cancer. Over the past 2 decades or so, this interaction has transitioned from a paternalistic attitude on the part of the physician toward the patient to an environment in which there is a shared decision-making process. Obviously, from the reading of this article, there is still much room for improvement. A new diagnosis of advanced ovarian cancer is generally very devastating, and there is an expected feeling of "loss of control" for the patient and her family. Because the standard management for a woman with suspected advanced ovarian cancer is primary cytoreductive surgery followed by combination chemotherapy, patients may feel that their options are very limited. One strategy for broadening treatment options for patients is to be able to offer innovative clinical trials, and much more work is needed to extend clinical trials into more community based practice settings. Elit et al use the comparison of this scenario to that of women with early-stage breast cancer, who are more easily able to assume a more autonomous role in decision-making regarding their treatment. There are several reasons for this disparity, including differences in average age, general condition, and the influence of prognosis on psychological well-being. Much more study is needed in this area, but we are continuously moving closer to the ideal in which patient preferences emerge as key components during this most sensitive time. ■

Special Feature

Alternatives to Menopausal Hormone Therapy

By Sarah L. Berga, MD

One of the benefits that has come from the release of the data from the Prempro® arm of the Women's Health Initiative (WHI) on July 9, 2002, has been a re-evaluation of the pros and cons of menopausal hormonal therapy. In undertaking this appraisal, one inevitably asks what are rational alternatives to hormone use. It is a very logical question. I think we have to accept that many, if not most, women and men want to do what they can to remain as well as possible for as long as possible. Aging gracefully is a worthy pursuit, and we need to find ways to aid those who attempt it. After all, it is a sign of mental health that one wants to minimize age-related disability and disease. However, it is not trivial to outline acceptable alternatives. Consider the following issues.

To delineate alternatives to postmenopausal estrogen or progestin use, one must first understand the benefits and risks of its use. The difficulty inherent in comparing postmenopausal hormone therapy with various alternatives is highlighted by the fact that hormone therapy does not constitute a single therapy. Indeed, although it is not commonly appreciated that each estrogen preparation has unique molecular and tissue effects, the same dose of a given estrogen or progestin does not lead to the same circulating levels in all women or in all tissues within that woman, and not all women stand to benefit equally or suffer the same risks and side effects from postmenopausal estrogen use. Further, progestins differ in their molecular and clinical profiles.

Given this enormous complexity and ever-burgeoning molecular insights, clinicians may feel stymied by a lack of reliable clinical data upon which to guide treatment decisions. Further, the adequacy and acceptability of alternatives to postmenopausal hormone use depend in part on the expectations and goals of therapy. If goals are circumscribed (such as treatment of osteoporosis), then it is easier to delineate several acceptable alternatives. If the goal is to produce in all tissues of relevance an estrogenic effect, but with an absence of estrogen action in tissues in which this effect is deemed deleterious, then that is a much more ambitious undertaking. In asking what might constitute acceptable alternatives to postmenopausal estrogen therapy, one could simply advocate a good lifestyle with an appropriate amount of exercise and an acceptable diet. Or one could advocate a good lifestyle ***plus*** periodic surveillance for disorders for which we have good treatment options, such as statins for dyslipidemia. This strategy involves waiting for a disease process to announce itself and then trying to intervene.

The problem is that most health-conscience individuals want to ward off age-related disease and disability before it becomes evident. This means prevention and prophylaxis. The ultimate goal is to ***retard*** the aging process. This is also a much more complex task than commonly assumed. While we can enumerate age-related disabilities and diseases, we still don't really understand what aging means at the molecular level. It is hard to imagine how we could reverse or retard a process that is so poorly understood. Fortunately we are making progress in understanding that ontogenic process we call aging. For those aficionados who love science at its best, try reading the February 28, 2003 issue of *Science*, which is devoted to illuminating the many dimensions of aging. In that issue, Juengst and colleagues urge that our scientific institutions must take the lead in ensuring that public discussion of anti-aging research is as deliberate and farsighted as the research itself. If there is one thing we learned from the WHI, it is that strategies advocated for retarding aging hold both promise and peril.

Agents commonly considered as alternatives to postmenopausal estrogen use for preventing age-related disability include selective estrogen receptor modulators (SERMs), phytoestrogens, black cohosh, other herbal agents, and some vitamins. Other "anti-aging" hormones include dehydroepiandrosterone (DHEA), androstenedione (Andro), melatonin, and growth hormone and its analogs. While acceptance of postmenopausal estrogen therapy has been constrained by recent evidence from the WHI, acceptance of alternatives is often buoyed by hypothetical benefits based on reductionistic assumptions about tissue effects or pathogenetic mechanisms, known benefit in a particular tissue such as bone without demonstrated efficacy in other tissues, and/or lack of long-term data regarding clinical outcomes. Indeed, the more an agent is studied, the more we find out about its risks and side effects. Often, putative benefits do not stand the test of time. The availability of untested or insufficiently tested agents coupled with negative perceptions regarding pharmaceutical estrogens makes counseling menopausal women a challenging task.

Despite the limitations of current strategies, our increasing longevity makes it imperative that we continue to search for ways to reduce the burdens of aging. While

we don't quite know why, there can be no doubt that we are on average living longer and longer. Although the field of anti-aging is in its infancy and our initial attempts look as clumsy as the first car or early computers, this line of investigation and intervention is here to stay. Today's task is to help patients understand the gap between expectations and our limited fund of knowledge. It is important for physicians and patients to recognize that we will be forever refining our approaches. Whatever strategies are undertaken will hold both promise and peril, because there is no easy and rapid way to acquire the knowledge needed to hold back the ravages of aging. ■

Reference

1. Juengst ET, et al. *Science*. 2003;299:1323.

CME Questions

12. Which of the following is *not* advocated for slowing the aging process?

a. DHEA
b. Bisphosphonates
c. Melatonin
d. Diet
e. Exercise

13. The following statements are true of the Women's Health Initiative *except*:

a. The WHI results apply only to its studied population.
b. The WHI population cannot assess the effect of hormone therapy on menopausal symptoms.
c. The WHI results apply to all postmenopausal women.
d. Politics, journalism, and medicine are a bad mix.

14. The following statements are true regarding oral contraceptives and hypertension *except*:

a. The two major factors that increase the risk of cardiovascular events in women who use oral contraceptives are smoking and hypertension.
b. Oral contraceptives can increase blood pressure.
c. Women with controlled hypertension can use oral contraceptive if they do not smoke and are otherwise healthy.
d. Women with controlled hypertension can use low dose oral contraceptives until menopause.

Answers: 12 (b); 13 (c); 14 (d)

Readers are Invited. . .

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PHARMACOLOGY WATCH

Counterfeit Procrit Uncovered by FDA Surveillance

In one of the more bizarre stories of the year, the FDA has uncovered files of counterfeit Procrit (epoetin alfa—Johnson & Johnson) in routine surveillance. To make matters worse, the fake vials have been contaminated with bacteria and many contain no active ingredient. Johnson & Johnson is sending out a "Dear Doctor" letter to warn health care professionals about the counterfeit vials including the lot numbers of the suspected counterfeits. Fake Procrit was also discovered last summer in United States. At that time, counterfeiters apparently purchased 2000 U/mL vials and labeled them as the higher priced 40,000 U/mL vials. More information is available at the Johnson & Johnson/Ortho Biotech web site including pictures of the counterfeit vials.

Pharmaceutical Marketing Campaigns in Full Swing

Love 'em or hate 'em, direct-to-consumer (DTC) advertisements of pharmaceuticals are big business. The Kaiser Family foundation reports that spending on DTC ads increased nearly 10-fold in 10 years, from $260 million to $2.5 billion in 2000. More than 80% of respondents report seeing or hearing a drug ad in the last 3 months according to an FDA survey, and the Kaiser study reports that one third of patients have asked their doctor about an ad they saw on TV or in print. Unfortunately, drug ads are increasingly unregulated. The FDA is tasked with reviewing DTC ads for false or misleading statements, but according to a recent review in *Consumer Reports*, the agency has only 30 reviewers to handle 30,000 submissions each year. By the time false or misleading ads are pulled from the airways, they have often run their lifespan, with new ads appearing in their place. But are the pharmaceutical companies getting $2.5 billion of value from these ads? Apparently. A recent FDA survey of physicians revealed that when patients initiate a discussion about a prescription drug they've seen advertised, they asked for a prescription more than 50% of the time. Some 66% of physicians said they were not pressured to prescribe a drug in that situation. However, when a specific brand name drug was requested, physicians felt pressured to prescribe it more than 50% of the time. Despite this, physicians are split on the effect of DTC ads on their patients and practice, with 32% feeling negative about the ads, 40% feeling positive, and 28% feeling that DTC advertising has no effect on the practice (www.fda.gov/cder/ddmac/presentations.htm).

Ambulatory Antibiotic Reduction: Take the Good with the Bad

The national campaign to reduce antibiotic use in ambulatory practice seems to be working, but there is good news and bad news. Researchers from UCSF and Harvard reviewed the rates of overall antibiotic use in the National Ambulatory Medical Care Survey between 1991-1992, and compared those rates to usage between 1998-1999. The use of antibiotics decreased in the latter time period especially for the treatment of respiratory tract infections such as the common cold and pharyngitis (visits with a

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prescription decreased from 13% to 10% in adults, and from 33% to 22% among children). The use of broad-spectrum antibiotics increased over the same time span; however, including the macrolides azithromycin and clarithromycin, quinolones, amoxicillin-clavulanate, and second- and third-generation cephalosporins. The use of these antibiotics increased from 24% to 48% of all antibiotic prescriptions among adults and from 23% to 40% among children. An accompanying editorial reiterates the CDC's Campaign for Appropriate Antibiotic Use in the Community, which encourages prescribing antimicrobials only when they are likely to be beneficial to the patient, selecting agents that will target the likely pathogen, and using these agents in the correct dose and for the proper duration. The editorial suggests that we have been effective at decreasing the overall use of antibiotics, but less successful at promoting targeted therapy, ie, using narrow spectrum antibiotics whenever appropriate to reduce the likelihood of resistance in a population (*Ann Intern Med*. 2003;138:525-533,605-606).

Nefazodone Under Attack Once Again

Public Citizen, the national nonprofit watchdog organization, has petitioned the FDA to remove the antidepressant nefazodone (Serzone—Bristol-Myers Squibb) from the US market. The petition is based on evidence of liver toxicity associated with the drug including liver failure and death. Nefazodone was recently pulled from the European market after reports of a worldwide total of 28 cases of liver failure of which 18 patients died. The move in Europe was voluntary on the part of Bristol-Myers Squibb because of the call for increased liver enzyme monitoring requirements in several European countries. In this country, the FDA has required a black box warning on nefazodone since January 2002. Despite these concerns, nefazodone, which is a SSRI antidepressant, continues to be relatively popular, with more than 4 million prescriptions written last year. Bristol-Myers Squibb has no plans to withdraw the drug in this country at present.

Lindane Receives Black Box Warning

The FDA has issued a Public Health Advisory concerning the use of lindane for the treatment of scabies and lice. The boxed warning is the result of concern of potential neurotoxicity especially in children. The new advisory states that lindane is a second-line treatment and updates information about its potential risk in children and adults who weigh less than 110 pounds. The advisory also states that reapplication of lindane lotion or shampoo is not appropriate even if itching continues after the single treatment. The FDA is also requiring package sizes to be limited to 1 and 2 oz in order to minimize the potential for product access in a single treatment. Lindane, also known as gamma benzene hexachloride, is an industrial pesticide, has been in use for decades, and has been banned in several countries. Neurologic side effects include dizziness, seizures, and even death. The drug is currently approved for the treatment of lice and scabies in patients who have failed or are intolerant of other therapies. First-line agents for scabies include permethrin cream (Nix, Elimite, Acticin) and malathion lotion (Ovide) and for lice pyrethrum with piperonyl butoxide shampoo and cream rinse permethrin cream rinse (Nix and Rid).

Aspirin Could Help Reduce Colorectal Adenomas

Two different studies in the same issue of the *New England Journal of Medicine* suggest that daily doses of aspirin reduce the risk of colorectal adenomas. In the first study, 635 patients with previous colorectal cancer were randomized to receive either 325 mg of aspirin per day or placebo. The study was terminated early when a significant reduction in colorectal adenomas was shown during the planned interim analysis. After an average of 12.8 months of follow-up, 1 or more adenomas were found in 17% of patients in the aspirin group and 27% patients in the placebo group ($P = 0.004$). The mean number of adenomas was lower in the aspirin group ($P = 0.003$) and the time to detection of the first adenoma was longer in the aspirin group than in the placebo group ($P = 0.022$). In the second study, 1121 patients with a recent history of adenomas were randomized to placebo (372 patients), 81 mg of aspirin (377 patients), or 325 mg of aspirin (372 patients). Follow-up colonoscopy was done approximately 3 years after randomization. The incidence of 1 or more adenomas was 47% placebo group, 38% in the 81 mg aspirin group, and 45% in the 325 mg aspirin group (global $P = 0.04$). The risk of larger polyps including adenomas measuring > 1 cm or with tubulovillous or villous, or severe dysplasia was also lowest in the 81 mg aspirin group. An accompanying editorial suggests that inhibition of COX-2 may prevent inflammation, increased cell proliferation and angiogenesis. The author also cautions that prophylactic aspirin is not a substitute for colorectal cancer screening (*N Engl J Med*. 2003; 348:883-890, 891-899,879-880). ■

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