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INSIDE

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Betamimetics in Pregnancy Related to Autism: Really?

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics and Gynecology, University of Colorado Health Sciences Center, Denver

Synopsis: *A recent review addresses the potential link between beta 2-adrenergic agonists in pregnancy and autism.*

Source: Witter FR, et al. In utero beta 2 adrenergic agonist exposure and adverse neurophysiologic and behavioral outcomes. *Am J Obstet Gynecol* 2009;201:553-559.

In the last two months, there were four articles in the *American Journal of Obstetrics & Gynecology* and *Obstetrics & Gynecology* dealing with drugs that are commonly used in pregnancy and their possible contribution to adverse outcomes. One of these articles was particularly attention-getting.

Witter et al reviewed the literature regarding possible adverse effects of beta 2-adrenergic receptor (B2AR) agents in pregnancy. This group of drugs can cause an overstimulation of these receptors, resulting in a disruption of the delicate balance between sympathetic and parasympathetic systems. By dampening the latter, mellowing mechanism, the sympathetic system is given free rein. Stimulation of B2AR has been shown in rats to have an effect on cells in the fetal cortex, cerebellum, and hippocampus that are similar to those found in humans with autism.[1]

The authors reviewed what data are available regarding a possible link between B2AR agents and autism:

- Some human studies have suggested an increased incidence of autism in children exposed to B2AR agents in utero.[2,3]
- One study linked maternal asthma with autism[4] (perhaps relating more to the treatment for asthma, rather than the condition itself).
- Some data have suggested a possible linkage between subnormal cognitive and motor performance in children and maternal exposure to B2AR agents, along with poor school performance in association with ritodrine, in particular.[5]

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- A greater tendency toward adolescent hypertension in those whose mothers were given ritodrine for preterm labor.[6]
- As to how much B2AR exposure would be needed to cause a possible problem, this can be difficult to assess, since some fetuses harboring a known B2AR polymorphism are likely to be more sensitive to the effects of these agents than others exposed to the same dose.

■ COMMENTARY

Current figures indicate that 1 in 110 children in the United States have some form of autism. Although some have interpreted this to suggest an alarming increase in the prevalence of this condition, this could be also due to a recent increased focus on documenting this condition. Whether this is new or old news, any condition that affects 1% of children is very concerning and has generated a search for a reason(s).

The above review has shed some light on one possible in utero mechanism, but there is obviously more to this story, especially since not all follow-up studies have shown an association between B2AR agents and autism. Nevertheless, we have to ask ourselves how necessary it is to use various forms of B2AR agents in pregnancy. The two most common reasons this type of medication has been used are for asthma and to stop labor.

Asthma. Here, B2AR agents are used primarily as bronchodilators. Since there is no doubt that unabated asthma is far worse for the fetus (and mother) than any current therapy, it is clear that some type of treatment is essential. In most cases, to limit fetal exposure time, one can preferably treat this condition with the shortest acting medications such as albuterol (which has a reasonable safety record), or to substitute a corticosteroid inhaler for treatment of mild intermittent asthma. Also, extrapolating from the rat model, the most vulnerable time in the neural development of the fetus is the last part of the second trimester and early third trimester.

Preterm labor. Beta 2-adrenergic agonists have been used as tocolytics for years. Interestingly, ritodrine is the only medication approved by the FDA for this purpose, yet terbutaline has been by far the most commonly used. Now, after many randomized trials, no B2AR has been shown to be beneficial in preventing preterm birth, although one study did show that ritodrine was better than placebo in prolonging pregnancy for 48 hours — long enough to get steroids on board. Terbutaline, administered in any form, has not been shown to lengthen pregnancy. However, anecdotally, oral terbutaline does seem to decrease the number of Braxton-Hicks contractions (thereby blunting patient anxiety and diminishing the number of telephone calls to providers).

So, based on current information, there seems to be no reason to use B2AR agents for tocolysis. Unfortunately, the labor-stopping track record of other drugs is not stellar, and virtually every substitute has its own possible maternal/fetal side effects. Our "go-to" drug now is a calcium channel blocker (nifedipine) or, in some cases, a prostaglandin synthetase inhibitor such as indomethacin (while watching for early signs of ductal closure).

In summary, as yet there has been no concrete evidence to directly blame autism on B2AR agents, since this unfortunately common condition undoubtedly evolves through many pathways. However, if one of these pathways can be avoided, why not err on the side of caution and use B2AR agents judiciously in asthma, and not at all in preterm labor. ■

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Questions & Comments

Call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468.

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Breast Tenderness, HRT, and Breast Cancer

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *New-onset breast tenderness in women using combined hormone replacement therapy is common, but this is not a useful predictor of future breast cancer risk.*

Source: Crandall CJ, et al. New-onset breast tenderness after initiation of estrogen plus progestin therapy and breast cancer risk. *Arch Intern Med* 2009;169:1684-1691.

THE AUTHORS ANALYZED DATA FROM THE WOMEN'S Health Initiative (WHI) combined Estrogen/Progestin Trial to determine if new-onset breast tenderness (NOBT) was associated with the development of breast cancer. The WHI combined group randomized postmenopausal women with an intact uterus to receive either daily conjugated equine estrogens (0.625 mg) plus medroxyprogesterone acetate (2.5 mg; Prempro®, CEE/MPA) or placebo, and followed a number of health outcomes including breast cancer. Breast tenderness was self-reported at baseline and at the 12-month follow-up visit via a symptom inventory. Breast cancer outcomes were self-reported every 6 months using standardized questionnaires, and breast cancer diagnoses were confirmed by local physician adjudicators who reviewed medical records and pathology reports. Significantly more subjects randomized to treatment with CEE/MPA (36.1%) than placebo (11.8%; $P = 0.001$) experienced new-onset breast tenderness after 12 months. Among subjects randomized to CEE/MPA, the risk of breast cancer was 48% higher in users with NOBT compared to users without breast tenderness (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.08-2.03). Breast cancer risk was not increased among women randomized to placebo with NOBT. However, when treatment assignment and NOBT were included in the same Cox regression model, the observed increase in risk was no longer statistically significant (HR, 1.29; 95% CI, 0.99-1.70). Using the less precise unadjusted figures, the authors calculated that NOBT had a sensitivity of 41%, a specificity of 64%, and a positive predictive value of 2.7% for the development of invasive breast cancer risk during the intervention period (mean, 5.6 years). The authors concluded that reports of breast tenderness during CEE/MPA therapy may identify women at high risk for the development of breast cancers.

■ COMMENTARY

Although this article was published last fall, it deserves some commentary as these studies tend to circulate back to our offices after being posted on internet sites or in women's magazines. Dr. Speroff passed it on to me, so I thought I would follow our former editor's advice and bring it to your attention.

The basis for the study rests on two observed associations: Breast cancer diagnosis and breast tenderness are both increased in women using hormone therapy. Hormone therapy also increases breast density on mammography. Since both of these findings reflect an increase in proliferation of breast tissue, there is reason for concern. Breast tenderness is a common finding in both postmenopausal and premenopausal women. In postmenopausal women, both HRT and ERT are associated with an increase report of breast tenderness. However, while the risk of breast cancer was increased in the WHI combined therapy study, no increase in risk was reported in the estrogen-only arm.[1]

Crandell and colleagues report a three-fold increase in new-onset breast tenderness among women in the combined arm of the WHI study.[2] This finding is nothing new. Breast tenderness is typically transient, going away after the first 3 months of therapy.[3] Persistent breast tenderness at 1 year is reported by about 25% of women starting HRT.[4] The type of HRT preparation may influence breast tenderness and density. Harvey reported that subjects randomized to transdermal combination therapy (50 µg E2/140 µg norethisterone acetate [NETA]) had lower rates of both breast tenderness (36% vs 58%) and increased mammographic density (61% vs 86%) than subjects using oral therapy (2 mg E2/1 mg NETA).[5]

In the paper by Crandell et al, subjects randomized to CEE/MPA that developed NOBT had a significant 48% increase in the risk of breast cancer compared to users that did not have breast tenderness. The risk of breast

cancer was not significantly increased among women randomized to placebo that developed NOBT, suggesting that hormone therapy was responsible for the boost. However, after adjustment for potential confounders in a Cox regression model, the magnitude of the effect decreased to 29%, and this was no longer statistically significant. Unfortunately, this adjustment is buried in the results section, and not presented in the abstract. An interesting side note in the WHI combined study was that despite randomization, women in the HRT arm had a significantly increased prevalence of breast tenderness at baseline compared to the placebo arm. While subjects with baseline tenderness were excluded from the present analysis, it is interesting to reflect on what impact this might have had to the overall comparison.

Increased density represents a concern if it reduces the sensitivity of mammography. As we discussed in the January 2010 issue of *OB/GYN Clinical Alerts*, mammography has a fairly high false-positive rate. For every 1000 women screened annually with mammograms starting at age 50, 95 will undergo "unnecessary" biopsies. Women accept this risk as regular mammograms provide a powerful reduction in the risk of breast cancer mortality. Seven fewer deaths from breast cancer will occur in the same 1000 women screened annually starting at age 50.[6] Another way to describe this relationship is the predictive value of a positive test (PPV); for mammography the PPV varies between 12% and 20%.[7] It was this relatively low PPV that led the United States Preventive Health Task Force to recommend against routine annual mammography. In the present study, new onset of breast pain was found to have a PPV of a breast cancer diagnosis of only 2.8%. Recall that the overall increase in breast cancer diagnosis is represented best in absolute terms, not in relative risk. Using the actual event rates and risk estimates from the WHI, for every 10,000 women treated with CEE/MPA, the absolute increase would be 8 additional breast cancer cases. If we conservatively follow the calculations in the Crandell paper, 24% of this increase (approximately 2 cases) would be "explained" by NOBT. Another way to explain this to patients is that about 3% of women with new-onset breast tenderness that persists at 1 year will develop breast cancer within 5.6 years, but 97% will not.

While women want to be proactive to protect themselves against cancer, sending false alarms can produce unnecessary anxiety. Since breast tenderness is most prominent during the first 3 months, and resolves in nearly two-thirds of patients by 1 year, the assertion that NOBT is a useful predictor of breast cancer is highly likely to needlessly alarm women and their doctors. Women that experience breast tenderness may discontinue therapy. While women worry about breast cancer, they are much more likely to die from cardiovascular disease. According to the Centers for Disease Control and Prevention, in 2006 the mortality rate for women due to breast cancer (26.9/100,000) was about 10 times lower than that for cardiovascular disease (282.4/100,000). Although the WHI showed an increase in the rate of cardiovascular disease in women using combined CEE/MPA, this same association was not seen in women without a uterus using CEE only.[1] Furthermore, data from prospective and case-control studies have shown a reduction in cardiovascular disease among women who initiate hormone therapy with the onset of menopause, and similar findings were observed among the subgroup of women in the WHI-HRT study that were recently menopausal.[8] These results, along with studies from animal models and surrogate markers of cardiovascular disease in women, suggest that early initiation of HRT might provide substantial protection against the No. 1 killer of women. Needlessly frightening women by linking a common symptom like breast tenderness to breast cancer takes us in the wrong direction.

So what clinically important message does this paper provide? I believe that clinicians should use these data to reassure patients that breast tenderness is a common symptom of hormone therapy. The tenderness usually goes away within 3 months, and is related to dose. Transdermal therapy may be associated with less tenderness and less dense breasts, and also has been shown to reduce the risk of venous thrombosis.[9] All postmenopausal women using HRT should undergo breast cancer screening with annual mammograms (so should those not on HRT). For the 25% of women who will complain of persistent breast tenderness after 1 year of therapy, the results of this study may apply. Your patients that are already fearful of hormone therapy may look at a 3% chance of breast cancer developing over 5.6 years and stop HRT. Patients that see the benefits of HRT might be reassured that they have a 97% chance that they won't develop breast cancer. While the basic recommendations for mammogram screening don't change, all of these women should be counseled about the importance of keeping to the screening schedule. ■

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Bethesda Guidelines for Lynch Syndrome Screening Appear to Improve the Amsterdam Criteria

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman is a consultant to GlaxoSmithKline, Eli Lilly Co., Abbott Laboratories, Sanofi-Aventis, and Pfizer, and serves on the speakers bureau for GlaxoSmithKline, Eli Lilly Co., and OrthoBiotech.

Synopsis: *The 1996 Bethesda guidelines (revised 2002), which were added to the Amsterdam criteria to improve screening sensitivity and specificity for Lynch syndrome, were evaluated relative to a diagnostic algorithm in two gynecologic populations supporting their utility.*

Source: Walsh CS, et al. Lynch syndrome among gynecologic oncology patients meeting Bethesda guidelines for screening. *Gynecol Oncol* 2009 Dec 22; Epub ahead of print.

LYNCH SYNDROME (LS) IS A FAMILIAL COLORECTAL cancer syndrome, which occurs as a result of autosomal dominant inheritance of DNA mismatch repair genes. It is characterized by a high lifetime incidence of colorectal cancer, as well as gynecologic malignancies, such as endometrial and ovarian cancer. Successful screening has been associated with decreased colorectal cancer mortality. The original 1996 Bethesda guidelines added two gynecologic populations for whom further evaluation should be entertained: those with endometrial cancer before the age of 45 years and those with two LS-related cancers (e.g., synchronous endometrial and ovarian cancer). Prevalence of LS and genomic characteristics for these populations is not well described and were the endpoints of the study. To address these endpoints, a diagnostic algorithm was constructed that included immunohistochemistry for mismatch repair protein expression, followed by selective evaluation for microsatellite instability and MLH1 gene promoter methylation. Among 72 eligible patients, 9 (12%) had molecular findings consistent with LS: 6/50 (12%) in the early-onset endometrial cancer group and 3/22 (14%) in the synchronous primary cancer group. In an additional 3 cases, MLH1 silencing was due to promoter methylation: 1/50 (2%) in the early-onset endometrial cancer group and 2/22 (9%) in the synchronous primary cancer group. Of the 9 women with molecular criteria suggesting LS, only 3 had pedigrees meeting the Amsterdam criteria. The authors conclude that a diagnostic algorithm can identify patients with LS and those who warrant further genetic testing. Their findings reinforce the recommendation that women diagnosed with endometrial cancer before the age of 45 years and women with synchronous endometrial and ovarian cancer be screened for LS, irrespective of family history.

■ COMMENTARY

The lifetime risk of developing endometrial or ovarian cancer in patients with Lynch syndrome is estimated at 60% and 12%, respectively. Despite the syndrome's relative rarity (annual incidence about 1/1000-2000), the identification of potentially affected individuals before a cancer diagnosis can lead to effective screening, which has not only been associated with reduction in LS-associated cancer, but also reduced mortality. In 1991, the Amsterdam criteria, commonly referred to as the "3-2-1 criteria" (i.e., 3 first-degree relatives with LS cancers, in 2 generations, 1 of whom developed cancer before age 50), were developed to assist patients and health care providers in identifying individuals and families at high risk for LS. In light of its low performance sensitivity, the guidelines were amended in 1996 and

again in 2002 to add other "at-risk" populations, including those individuals developing endometrial cancer at an early age and those with dual, or "synchronous," primaries, such as in the uterus and ovaries simultaneously. While believed to improve specificity and sensitivity, the prevalence of genomic changes in these populations has been infrequently described and was evaluated in the current study. Young age at diagnosis and synchronous primaries in the uterus and ovary have been previously represented by a small, but important fraction (5%-15%) of LS-associated genomic changes. The current study also demonstrates the latter group is frequently associated with MLH1 epigenetic change, notably promoter methylation, and as such, alone, would not require further evaluation for LS in family members. This indicates that patients found with tumors lacking immunohistochemical staining for MLH1 protein should be additionally screened for epigenetic change. Finally, in this, as in other recent studies, family history proved to be an unreliable triage tool, suggesting heightened clinical awareness be exercised in identifying potential subjects. ■

Additional Reading

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Special Feature

Robotic Surgery: Time to Do Some Soul-searching

By Frank W. Ling, MD

Clinical Professor, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

Dr. Ling reports no financial relationship to this field of study.

DATA CONTINUE TO BE GENERATED RELATED TO THE use of robotic surgery in gynecology. At the current time, what the future holds for this latest technology within our specialty is anyone's guess. That does not mean, however, that the individual physician should ignore it until the data are conclusive. Indeed, if a clinician had waited to see what role laparoscopic-assisted vaginal hysterectomy played relative to abdominal and vaginal hysterectomy, that individual would still be waiting for the final answers. That impact continues to evolve. Laparoscopic hysterectomy rates have increased from 0.3% in 1990 to almost 12% in 2003. This has, in turn, been accompanied by a reduction in the proportion of abdominal cases and a slight increase in hysterectomies performed vaginally.

The purpose of this article is to provide the thoughtful gynecologic surgeon an opportunity to reflect on how he/she will approach the possible incorporation of what is clearly an innovation that can potentially alter how gynecologic surgery is performed in an individual's practice and/or hospital. As one might expect, the actual performing of the procedure is only the tip of the iceberg, as non-medical factors — be they economic, educational, and ethical — enter into the final decision the clinician will make.

The Technology

The da Vinci Surgical System was introduced in 1999 and was granted FDA approval for gynecologic surgery in 2005. Both advantages and disadvantages are acknowledged.

Potential advantages of robotic surgery:

- Three-dimensional visualization improves depth perception
- Improved dexterity replicates full range of motion of surgeon's hands
- Increased precision through elimination of physiologic tremors
- Reduced fatigue from surgeon being seated at the console
- Shorter hospital stays using minimally invasive approach

Potential disadvantages of robotic surgery:

- Higher cost, including > $1 million initially, and disposables
- Increased operating time due to equipment set-up time
- Lack of tactile feedback to the surgeon
- Inability to reposition patient after robot arms attached
- Bulkiness of operating system and lack of vaginal access

Surgical Procedures

Potential cases for which the robotic technology is currently appropriate is based upon the experience of others who have published on their respective experiences. Simple hysterectomy is one of the most common procedures and is proposed as an example of a case that is more difficult for a laparoscopic approach, but may be accomplished robotically without having to resort to laparotomy. Myomectomy has also been aided by the robotic approach. Pelvic reconstruction, with particular emphasis on sacrospinous fixation, as well as gynecologic oncology cases, has also been shown to be potential areas in which robotic technology can be beneficial. In tubal reanastomosis, robotic surgery apparently takes longer, but is comparable to mini-laparotomy in terms of hospitalization duration, ectopic pregnancy rates, and pregnancy rates. Convalescence is shorter with robotic surgery.

Educational Issues

The impact of robotic surgery has not only clinical aspects, but educational ones as well. Both anecdotal and published data suggest that how residents are trained is already being affected by the technology. At one institution in Michigan, hysterectomy rates for the 18 months prior to the introduction of robotic surgery were compared to the 18 months after; it was found that there was a statistically significant reduction in the rate of laparoscopic-assisted vaginal hysterectomy as well as total abdominal hysterectomy. With fewer traditional cases available to residents, the need for the attending physician to attain a level of comfort with the technique, and minimal meaningful clinical experience for the resident/assistant surgeon, the implications for the training of gynecologic surgeons of the future are obvious.

That being said, the challenge for the education of the individual surgeon who is beyond residency and already in practice is no less daunting. Merely starting to do the procedures without appropriate training and preparation is certainly inappropriate. The education/training of the surgeon should be done in coordination with an operating room team if there is not one already. A mandatory course is available involving dry labs and animal models, but having a proctor present for the first several cases is a must. Initially, patient and case selection are critical to build an appropriate track record and case load. The days required to obtain the education as well as the additional hours required to perform the initial cases before greater expertise is obtained must be looked at carefully for the surgeon to determine whether it is worth the time and effort invested into a technology that he/she may or may not enthusiastically embrace.

Economic Issues

The time needed to become educated in the technology and use thereof is not insignificant. As the old saying goes, "Time is money." Will the time invested result in rewards that are of sufficient value? Each clinician will need to answer that for him/herself since the return on investment may or may not take the form of more patients (and implicitly more cases), more peer recognition, more job satisfaction, etc. By the same token, the economic issue for the surgeon may be moot if the hospital chooses not to invest in the technology. Often, multiple specialties together may have to press for this significant capital expenditure.

All surgeons considering becoming a robotic surgeon should certainly ask whether the driving force is truly wanting to deliver better care to the patient or just to "keep up with the Joneses." In some markets, the perception of who the best gynecologic surgeons are is based not on expertise, but on whether they offer the latest surgical approach.

Ethical Issues

Since there is only one manufacturer, any case done with the robot, is, by definition, done with their machine. This monopoly on the equipment side makes for an interesting dynamic as the technology is being considered. How much is being offered as helpful to the patient and how much is actually a sale? For now, there are precious few data that definitively demonstrate the superiority of the robotic approach over more traditional techniques. In fact, one cannot help but recall the questions raised when laparoscopic-assisted vaginal hysterectomy was sometimes referred to as "a procedure looking for an indication."

Without question, our first priority must be to the welfare of the patient. Are we improving her health? Are we putting her at risk? Is she getting our best? Is she getting full informed consent? Are you prepared to tell her that you've only done it this way a few times?

If the commitment is made to become a robotic surgeon, then it's incumbent upon the clinician to keep up with the robotic literature and attend postgraduate courses and hands-on workshops. A commitment to excellence to this surgical approach is no different from keeping up skills in any other area of practice we participate in, i.e., obstetrics, hormone therapy, health care screening, etc.

The Challenge

So there it is, the challenge to each of us. A final decision is not necessarily needed now, but attention should be paid. The debate is just getting started and each of us

is going to have to take sides … eventually. "I've always done it this way" may well be your response to the challenge right now. I encourage you to accept the challenge to start deciding how you feel about it. Will you do it? Will you assist your partners who want to do it? Will your practice designate one partner to be the robotic surgeon? Will you help the hospital make the decision?

You won't know how to answer unless you keep an open mind and an inquiring one at that. We all committed ourselves to lifelong learning when we earned our medical degree. We owe that to each of our patients. The issue of robotic surgery is no exception. ■

Suggested Readings

1. Robot-Assisted Surgery: ACOG Technology Assessment in Obstetrics and Gynecology. *Obstet Gynecol* 2009;114:1153-1155.
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CME Questions

43. Which of the following answers is the most appropriate?
a. Some studies have shown an increased rate of autism in those whose mothers were given B2AR agents.
b. Autism has been possibly linked with asthma.
c. Studies have shown brain changes similar to those found in autism when rats are exposed to B2AR agonists.
d. All of the above

44. Which of the following is the most appropriate statement?
a. Terbutaline has been proven to lengthen pregnancy.
b. Ritodrine has been shown to lengthen pregnancy.
c. Ritodrine is the only betamimetic agent approved by the FDA.
d. Betamimetics work better then steroids in promoting fetal lung maturity.

45. What percentage of women with endometrial cancer and molecular criteria suggesting Lynch syndrome had a family history meeting the Amsterdam criteria?
a. 0%
b. 33%
c. 50%
d. 67%

46. Which of the following was *not* a factor used to match the controls to the cases in this study by Walsh et al?
a. Smoking
b. Age
c. African-American ethnicity
d. Availability of blood

Answers: 43. d, 44. c, 45. b, 46. a.

CME Objectives

Upon completion of this educational activity, participants should be able to:
- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

In Future Issues:

Biomarker Lead Time: Are We There Yet?

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Hospital Medicine Alert, Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Oral Treatments for Relapsing-remitting MS

In this issue: Two oral medications for relapsing-remitting MS in phase III development; antihypertensives find new uses; *Ginkgo biloba* does not prevent cognitive decline in elderly; and FDA Actions.

Oral medications for relapsing-remitting MS

Two new oral medications are effective treatments for relapsing-remitting multiple sclerosis (MS) according to three studies published on-line in the *New England Journal of Medicine*. Fingolimod and cladribine differ in the mechanism of action but both reduce the number of potentially auto-aggressive lymphocytes that are available to enter the central nervous system. In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial, two different doses of cladribine were compared to placebo with the endpoint being relapse at 96 weeks. Both doses were more effective than placebo at preventing relapses and reducing brain lesion count on MRI ($P < 0.001$ for all comparisons). The drug was associated with lymphocytopenia and a higher risk of herpes zoster.

Fingolimod was compared to placebo in the FREEDOMS trial and compared to injectable interferon in the TRANSFORMS trial. The 24-month FREEDOMS trial compared two doses of fingolimod to placebo and similarly found a lower rate of relapse ($P < 0.001$ for both doses) and disability progression ($P = 0.02$ for both doses). The drug also reduced the number of new lesions found on MRI. Significant side effects included bradycardia, AV block, macular edema, elevated LFTs, and mild hypertension. When compared to interferon, fingolimod was associated with significantly lower annualized relapse rates at both doses tested ($P < 0.001$ for both comparisons), although there was no significant difference with respect to progression of disability. Two fatal infections occurred with the higher dose of fingolimod (disseminated primary varicella zoster and herpes simplex encephalitis). (All three studies published on-line at www.NEJM.org, Jan. 20, 2010).

An accompanying editorial calls the arrival of oral formulations of MS drugs "welcome news for the estimated 2.5 million people worldwide with this chronic, disabling disease." While suggesting these drugs "support a change in treatment approach to directly prevent immune-related injury," the editorial also suggests that long-term goals of MS therapy are currently lacking (published online at www.NEJM.org, Jan. 20, 2010). Both drugs are in phase III trials for treatment of MS; cladribine is currently approved in parenteral form for treatment of hairy cell leukemia. ■

Antihypertension drugs for AF and dementia?

Different classes of blood pressure (BP) medications may have different benefits according to two new studies. In the first study, researchers from the United Kingdom performed a nested

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case-control analysis to evaluate whether different antihypertensive drug classes may alter the risk for atrial fibrillation. The researchers reviewed records from a large patient population, specifically patients who were on a single agent for lowering BP. A lower odds ratio (OR) for atrial fibrillation was noted with ACE inhibitors (OR, 0.75; 95% confidence interval [CI], 0.65-0.87), angiotensin receptor blockers (ARBs) (OR, 0.71; 95% CI, 0.57-0.89), and beta-blockers (OR, 0.78; 95% CI, 0.67-0.92) compared with current exclusive therapy with calcium channel blockers. Although the researchers were unable to assess why patients were receiving one class of blood pressure medicine over another, they concluded that long-term therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for atrial fibrillation compared with calcium channel blockers. These findings generally relate to patients with mild hypertension, since patients on multiple drugs were excluded from the study (*Ann Intern Med* 2010;152:78-84).

In the second study, researchers from Boston set out to investigate whether ARBs reduce the risk of Alzheimer's disease and dementia or reduce the progression of both diseases. More than 800,000 predominately male participants, age 65 or older with cardiovascular disease, were studied. Patients were divided into three cohorts (ARBs, lisinopril, and other cardiovascular drugs as a comparator) and followed over 4 years, with adjustments for age, diabetes, stroke, and cardiovascular disease. Hazard rates for dementia in the ARB group were 0.76 (95% CI, 0.69-0.84) compared to the cardiovascular comparator, and 0.81 (95% CI, 0.73-0.90) compared to the lisinopril group. In patients with pre-existing Alzheimer's disease, ARBs were associated with significantly lower risk of admission to a nursing home. The combination of the ARB and ACE inhibitor was better than ACE inhibitor alone in preventing dementia and reducing admission to nursing home. The authors conclude that ARBs are associated with a significant reduction in the incidence and progression of Alzheimer's disease and dementia compared to ACE inhibitors or other cardiovascular drugs (BMJ 2010;340:b5465, doi: 10.1136/bmj.b5465, published on-line Jan. 12, 2010). An accompanying editorial points out that several studies have shown that treatment with any antihypertensive is associated with a lower risk of cognitive decline or incident dementia in older adults. What is not clear is whether some antihypertensives also have other biological mechanisms that help prevent dementia. It is plausible that ARBs are more neuroprotective than other drugs because of their effect on type 2 angiotensin receptors in the brain (*BMJ* 2010:340;b5409, doi: 10.1136/bmj.b5409, published on-line Jan. 12, 2010). ■

Ginkgo does not prevent cognitive decline

The National Center for Complementary and Alternative Medicine (NCCAM) was founded during the Clinton administration as part of the National Institutes of Health to investigate complementary and alternative medicines. Many of the NCCAM-funded studies, however, have shown no benefit from complementary or alternative treatments, and that is the case with a new study looking at *Ginkgo biloba* and cognitive function in older adults. *Ginkgo biloba*, which is widely marketed as an aid to preventing cognitive decline and dementia, was previously found to have no benefit in reducing the incidence of Alzheimer's disease or dementia overall (*JAMA* 2008;300:2253-2262).

In a new study sponsored by NCCAM, researchers set out to determine whether *Ginkgo biloba* slows the rate of global or domain-specific cognitive decline in older adults. More than 3000 participants age 72-96 years were enrolled and randomized to *G. biloba* 120 mg or placebo twice daily. Rates of change over time in two different objectives cognitive tests, as well as neuropsychological tests, were the primary endpoints. There was no difference in the decline in cognitive scores between *Ginkgo biloba* and placebo in any of the domains including memory, attention, and visuospatial abilities, language, or executive functions. There was also no difference in the rate of change in the standardized cognitive exams. The authors conclude that compared to placebo, *Ginkgo biloba* did not result in less cognitive decline in older adults (*JAMA* 2009;302: 2663-2670). ■

FDA Actions

Novo Nordisk has received approval to market liraglutide, a once-daily injection for the treatment of type 2 diabetes in adults. The drug is a glucagon-like peptide-1 receptor agonist similar to exanatide (Byetta®). The company is required to perform additional post-marketing cardiovascular studies as well as a 5-year epidemiological study to evaluate the risk of thyroid cancer. Liraglutide will be marketed under the trade name Victoza®. ■