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## INSIDE



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# Long-term Results with Tamoxifen in Prevention of Breast Cancer

ABSTRACT & COMMENTARY

***By Leon Speroff, MD, Editor***

***Synopsis:*** *The risk of estrogen receptor-positive breast cancers is reduced for at least 10 years after treatment with tamoxifen.*

**Source:** Cuzick J, et al. Long-term results of tamoxifen prophylaxis for breast cancer-96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst.* 2007;99:272-282.

The Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial began in 1986, enrolling 2,471 women with a positive first-degree family history of breast cancer.[1] The treatment group received 20 mg tamoxifen daily for 8 years. Twenty years later (median follow-up of 13 years), there were 139 estrogen receptor-positive breast cancers for a 39% reduction (HR = 0.61; CI = 0.43-0.86). The lowered risk did not become statistically significant until after the 8-year treatment period. The International Breast Cancer Intervention Study (IBIS) was also a randomized, double-blinded trial, beginning in 1992 and enrolling 7,145 women, but the treatment period with tamoxifen 20 mg daily was 5 years.[1] After a median follow-up of 8 years, there was a 34% reduction in estrogen receptor-positive cancers (RR = 0.66; CI = 0.50-0.87). The Royal Marsden trial found the reduction only after the treatment period. The IBIS trial found a greater reduction during the treatment period, but when the analysis was restricted to estrogen receptor-positive cancers, the two trials were similar, finding a greater effect after treatment.

## COMMENTARY

There have been four randomized placebo-controlled tamoxifen prevention trials. The American trial reported a significant 43% reduction in estrogen receptor-positive cancers.[2] The International Breast Cancer Intervention (IBIS) Study found a 32% reduction when invasive and ductal carcinoma *in situ* were combined, also only in estrogen receptor-positive tumors.[3] Follow-up of the Italian national trial demonstrated a reduction

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of estrogen receptor-positive cancers in the group of women considered to be at the highest risk of cancer. The Royal Marsden Trial in England demonstrated no reduction in breast cancer in the initial report.[4] The differences among these trials has been attributed to variations in risk factors in the studied populations. The American trial enrolled women with risk assigned by the Gail model. The women in the International trial were at a lower risk than those in the Royal Marsden trial, and the women in the Italian trial were not assessed for risk.

These long-term follow-up reports indicate that tamoxifen prevention of estrogen receptor-positive breast cancer in high-risk women lasts for many years after the treatment period. However, the long-term follow-up of tamoxifen-treated women continues to indicate an increase in cataracts, venous thrombosis, and gynecologic side effects (vasomotor symptoms, hysterectomy, endometrial cancer, and vaginal discharge), predominantly during the period of treatment.

Interestingly, the Royal Marsden trial (the American trial is the only one not to allow limited hormone therapy) could not detect any effect of hormone therapy on the results. However, the IBIS trial found that in women who used concurrent hormone therapy during the trial, no tamoxifen effect could be demonstrated; a finding, although limited by small numbers, that would be consistent with tamoxifen's antiestrogenic mechanism of action. It should be emphasized that hormone therapy is ineffective for the treatment of hot flushes associated with tamoxifen treatment.[5]

There is one lingering concern. There has been a slight increase in estrogen receptor-negative cancers in the follow-up period after treatment in all of the prevention trials. It is uncertain if this is related to tamoxifen exposure; however, in the trials assessing tamoxifen treatment of breast cancers, survival and recurrence rates worsened with longer therapy, probably due to the emergence of tamoxifen-resistant tumors. There are several possible explanations for resistance (such as tamoxifen stimulation of growth factor, and whichever of these are operative, it is believed that a subpopulation resistant to tamoxifen is present from the beginning, and over time grows to be clinically apparent.[6]

In conclusion, tamoxifen exposure for 5 to 8 years is associated with about a 30% to 40% reduction in estrogen receptor-positive breast cancers for at least 15 years after the treatment ends. An estimate of the absolute impact puts this in better perspective. The absolute reduction in cumulative overall incidence of breast cancer after 5 years is estimated to about 1.1% and after 10 years, 1.7%. This small impact combined with the serious side effects have made tamoxifen treatment an unattractive option. Note that there has been no differences in mortality rates comparing treatment and placebo groups in the prevention trials. We await the results of the prevention trials with aromatase inhibitors, anticipating even greater efficacy and a lower rate, if not an absence, of serious side effects. ■

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# Intravenous Bisphosphonate and Facial Bones

ABSTRACT & COMMENTARY

***By Leon Speroff, MD, Editor***

***Synopsis:*** *IV bisphosphonate treatment is associated with an increased risk of inflammation in the bones of the jaw and face.*

**Source:** Wilkinson GS, et al. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. *J Natl Cancer Inst.* 2007;99:1016-1024.

WILKINSON AND COLLEAGUES FROM THE University of Texas in Galveston analyzed information from the Surveillance, Epidemiology, and End Results (SEER) databank linked to Medicare claims.[1] There, 16,703 cancer patients were identified who were treated with IV bisphosphonates (pamidronate and zoledronic acid) from 1995 to 2003. When 14,349 treated patients were matched with 28,698 controls, the treated group had a 3-fold increased risk of jaw or facial bone surgery (HR = 3.15; CI = 1.86-5.32) and a very large increased risk of osteomyelitis of the jaw (HR = 11.48; CI = 6.49-20.33). The estimated absolute risk equaled 5.48 events per 100 patients over 6 years. In addition, the risk increased with increasing cumulative dose.

## COMMENTARY

By now the link between bisphosphonates and jaw osteonecrosis is accepted even though the previous studies contained small numbers. It is acknowledged that this is a relatively rare complication. The mechanism is uncertain beyond the recognition that infection and blood flow changes are involved. It is postulated that compromised healing ability of bone because of inhibition of bone turnover leads to a sequestered osteomyelitis and necrosis. This study is of importance because of its large size, and it confirms the earlier reports. Yet despite its size, the number of cases is not great enough to provide an estimate of the exact relative risk (note the wide confidence intervals indicating imprecision, usually due to small numbers).

Previous studies have suggested that the risk of osteonecrosis of the jaw is greater in patients treated with zoledronic acid compared with pamidronate.[2-4] Unfortunately, because of a delay in issuing a separate billing code for zoledronic acid, this question could not be addressed in this large cohort study.

The study also examined a large list of risk factors (such as different types of cancers, the presence of other medical conditions, the use of other drugs) and could find no associations with specific factors.

Awareness of this problem has led to increased attention to oral hygiene and the avoidance of tooth extractions in the high risk population of cancer patients receiving this treatment. The infrequency of this problem does not outweigh the substantial reduction in fractures and the need for irradiation or surgery of bone metastases in treated patients. But there remains the important question of the prevalence of this complication in individuals being treated for osteoporosis or the prevention of bone loss. Patients receiving bisphosphonate treatment for osteoporosis, with no history or evidence of malignancy, have experienced jaw osteonecrosis.[4,5] Clinical judgment suggests the following guidelines:

1. Duration of exposure to bisphosphonate should be limited, avoiding high local dosage secondary to the liberation of tightly bound bisphosphonate combined with on-going treatment. Many clinicians recommend discontinuation after 5 years with resumption of treatment when bone loss is demonstrated.
2. Avoid combining two anti-resorptive agents (even though there may be a small additional gain in bone density, there is no evidence that an additional benefit on fracture risk is achieved).
3. Think twice before treating young postmenopausal women with a bisphosphonate. ■

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# Manual Rotation in Occiput Posterior or Transverse Positions—Risk Factors and Consequences on the Cesarean Delivery Rate

ABSTRACT & COMMENTARY

***By John C. Hobbins, MD***

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

*Dr. Hobbins reports no financial relationship to this field of study.*

***Synopsis:*** *This paper resurrects a technique that has gotten little recent attention—second stage manual rotation for fetuses in the occiput posterior or transverse positions.*

**Source:** Le Ray C, et al. Manual rotation in occiput posterior or transverse positions. *Obstet Gynecol.* 2007;110(4):873-879.

The author reviewed a year's worth of data from a busy hospital in France where manual rotation was liberally used. The procedure, which will be described below, was used in 796 patients, in whom 85 (9.7%) failed. In 17 patients in the "failure" group the charts were uninterpretable, leaving data from the remaining 68 to be compared against data from 79 randomly chosen charts from the "success" group (controls).

The results were very enlightening. The operators were no more successful when fetuses were in the occiput transverse (OT) positions than in the occiput posterior (OP) positions. Of the 79 successes 70% occurred with one attempt. When 4 or 5 attempts were utilized none succeeded. If the rotation was attempted before full dilatation (in 20% of cases), there was a 3-fold greater chance of failure than if it was attempted at full dilatation.

Most importantly, Cesarean delivery occurred in 58.8% of the "failed" group vs 3.8% in the "successful" group. Epidural had little effect on the study results since 98% of the patients had them. There were no differences in Apgar scores and maternal morbidity between groups. All of the "failures" who delivered vaginally remained in a posterior position and the all of the "successes" stayed in an anterior position.

## COMMENTARY

Although there is a potential for bias in the study dealing with variability in operator skills and appropriateness of controls, one cannot help but be impressed with how much the Cesarean section rate was diminished in those having successful rotations. Certainly, the indigenous Cesarean section rate in patients with persistent posterior positions is very high, and there is evidence of higher rates of pelvic floor damage in patients delivering vaginally with fetuses in this position. Therefore, it would seem to make sense in those progressing sluggishly in the second stage to give it a try.

The technique described in the paper is as follows: With the patient on her back, if the head is in an LOP or LOT position, the right hand is gently inserted (or if not, two fingers) behind the ear between contractions. Then, during a contraction with the patient pushing, an attempt is made to rotate the head counterclockwise. If the fetus is in an ROP or ROT position, the left hand is used and the head is rotated in a clockwise direction. Obviously, if the maneuver causes a worrisome change in the fetal heart rate, one desists. The author seemed to be occasionally successful on the second and third attempts, but not with more attempts.

Many certified nurse midwives have advocated having patients with "posterior" labor in the hands and knees position, which still could lend itself to a rotation attempt, especially if the fetus is in a ROP position and the operator is very right-handed. ■

# Surgical Management of Primary Dysmenorrhea: Anything New?

ABSTRACT & COMMENTARY

***By Frank W. Ling, MD***

*Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville*

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

***Synopsis:*** *Presacral Neurectomy (PN) in combination with laparoscopic uterosacral neurectomy (LUNA) is no better than LUNA alone in the treatment of primary dysmenorrhea.*

**Source:** Juang C, et al. *J Reprod Med.* 2007;52:591-596.

In a study of 82 patients with primary dysmenorrhea who had been randomized to undergoing

either LUNA or LUNA + PN, the two groups had comparable results (69% improved in the LUNA group; 73% in the LUNA+PN group) at up to 12 months of follow-up. LUNA + PN was associated with more surgical complications including 16% of patients developing long-term constipation.

## COMMENTARY

After reading the summary of the article, it would be easy for the reader to dismiss this paper as being just a re-hash of what we have known for years, ie, uterosacral nerve ablation may or may not be of value in the treatment of primary dysmenorrhea, and that presacral neurectomy, given its potential risks, is not worth adding on as an additional procedure. You would be correct, but only partially so, and the way in which these Taiwanese investigators reached their conclusions is a lesson in good science as well as a lesson in how we can practice better medicine.

First, the authors ran a specific, rigorous protocol for 5 years. The necessary power analysis had been done so that they knew the number of patients theoretically required for a proper study. The study design was based on an assumption of 25% increase in surgical response (70 to 95%). The 70% baseline response was appropriately based on the expectation from the literature that there would be a 70% response rate. Their dedication to the study design is both laudable and the source of some of the strength of the science.

Second, the patients were first treated with nonsteroidal anti-inflammatory drugs and hormones. This is certainly a necessity for good science, just as in our daily practices. Surely, none of us would consider surgery for a patient with dysmenorrhea without first trying nonsteroidals and hormones. Admittedly, the lack of specificity in this aspect of the study bothered me since the specific nonsteroidal and the type of hormone were not described. Again, I suspect that in our respective practices, the use of one or more agents to suppress ovulation, ie, usually oral contraceptives, would be needed before discussing surgery.

Third, patients were subjected to a thorough evaluation of other conditions which might have been the cause of dysmenorrhea, ie, the protocol excluded patients with secondary dysmenorrhea. All too often, as in the literature on dysmenorrhea, not enough attention is paid to ruling out confounding variables. The authors here specify conditions such as endometriosis, adenomyosis, fibroids, pelvic trauma, irritable bowel syndrome, and interstitial cystitis. In our respective practices, each of us hopefully has a regular methodology by which we ask about possible gynecologic and nongynecologic causes of cramping pain. As I have mentioned in this space previously, I use the GUMP model to remember the common nongynecologic causes of pain (G for gastrointestinal, U for urogynecologic, M for muscular, and P for psychiatric).

Fourth, a standardized measure for pain was utilized. Unlike older studies, this one was able to compare apples with apples and oranges with oranges by making sure that the instrument used to measure the dysmenorrhea was validated. This increases the scientific rigor of this clinical investigation.

Fifth, the authors excluded subjects who had any anatomic conditions seen at initial laparoscopic evaluation. This was a final check to make sure that patients with adhesions, endometriosis, unsuspected fibroids, etc. were not being included in the study. Again, this makes the purity of the data that much greater.

Sixth, there was no surgery performed other than LUNA and PN. Again, this demonstrates that they knew the weaknesses of older studies in which patients might have undergone extensive lysis of adhesions or excision of endometriosis, etc. By keeping the procedures well-defined, much less confounding occurred.

Seventh, once a patient was considered appropriate, the surgical procedure was standardized such that the number of ports used and the technique applied was the same for each patient. The importance of this aspect of the study is critical since this is the actual intervening variable in this study.

Eighth, at each postoperative assessment, patients were assessed by 2 different reviewers who were blinded to the procedure. Certainly in our practices, we can't blind ourselves to what was done on our own patients, so the independent assessments here are a feature that should not be undervalued. So not only were the reviewers blinded, but a third reviewer was brought in if there was a discrepancy between the first two.

Ninth, the results teach us much about clinical medicine. The LUNA+PN group had more postoperative pelvic pain, bleeding, volume, hospital stay, and both short- and long-term constipation with 15% of the group requiring long-term laxative use. In both groups, there was a 6% incidence of urinary urgency or frequency but none of these symptoms were deemed long term. What does this tell us? First, patients should be given truly full informed consent regarding the potential of risks relative to the proposed benefits. Second, the procedures can be done in a timely fashion (average 21 minutes for LUNA and 38 minutes for LUNA+PN). The outcomes, howev-

er, suggest that the additional time and risk for the PN are unlikely to be warranted.

I guess you can tell that I really liked the paper's construction as well as the outcome. How can someone like the results of a study? It's because it validated what I have tried to do in my practice. The study design was a reflection of what I try to do with each of my patients. The choice of surgery in my decision-making process parallels that of this study. I'm not a big fan of PN, but I do recognize the potential (not promise) of LUNA and that is how I couch my recommendations with the patients.

My challenge to you is similar. Compare this paper with how you practice. Compare other clinically-applicable papers to your practice. When peer-reviewed articles are read, the editors of journals are hopeful that the SCIENCE of a large number of patients is applied to the ART of an individual patient. It works for me here, that's for sure. ■

# SGO's Statement on Risk Assessment for Inherited Gynecologic Cancer Predisposition

ABSTRACT & COMMENTARY

***By Robert L. Coleman, MD***

*Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston*

*Dr. Coleman reports no financial relationship to this field of study.*

***Synopsis:*** *Women with germline mutations in the cancer susceptibility genes, BRCA1 or BRCA2, associated with Hereditary Breast/Ovarian Cancer syndrome, have up to an 85% lifetime risk of breast cancer and up to a 46% lifetime risk of ovarian cancer.*

**Source:** Lancaster JM, et al. Society of Gynecologic Oncologists Education Committee Statement on Risk Assessment for Inherited Gynecologic Cancer Predispositions. *Gynecol Oncol.* 2007;107:159-162.

Germline mutations in BRCA1 or BRCA2 associated with the Hereditary Breast/Ovarian Cancer syndrome have an increased lifetime risk for breast (up to 85%) and ovarian (up to 46% BRCA1, up to 27% BRCA2) cancer. Likewise, women with germline mutations in the DNA mismatch repair genes, MLH1, MSH2 or MSH6 associated with the Lynch/Hereditary Non-Polyposis Colorectal Cancer syndrome have an increased risk of colon (up to 60%), endometrial (up to 60%) and ovarian (up to 12%) cancer. The dramatic association between cancer risk and mutation carriage exemplifies the importance of subject identification. Fortunately, genetic counselors are now widely available to provide accurate risk assessment and make appropriate recommendations to screening, surveillance, genetic testing and even surgery. However, patients must be identified in whom these services will be of merit. The SGO Education and Resource Panel for Hereditary Cancers, with approval of the Executive Committee of the Society of Gynecologic Oncologists, constructed the current document to aid healthcare providers in the identification of patients who may benefit from cancer risk assessment for these two major syndromes.

## COMMENTARY

The association between cancer development and carrier status of a germline mutation in one of the cancer susceptibility genes is provocative enough to recommend prophylactic surgery in some cases. The medical and emotional impact accompanying this decision-making process is obvious and best addressed by individuals with the necessary time and expertise to inform patients and their families as to their options and the consequences to their decisions. However, the process begins with discovery. The "Statement" was drafted and distributed to inform health care providers of those personal and familial characteristics that are associated with accelerated cancer risk. Importantly, the Statement draws attention not only to the well-understood breast and ovarian cancer association but also to the endometrial cancer predisposition in patients with the Lynch/Hereditary Non-Polyposis Colorectal Cancer syndrome. Patients with the latter syndrome are as likely to have an index case of endometrial cancer as they are to have colon cancer—a finding surprising to many unfamiliar with the genetic aberration and subsequent cancer profile. Indeed, affected family members also carry a 10% risk of ovarian cancer.

Healthcare providers are encouraged to make a detailed assessment of family history as part of their patients' personal medical survey. Posted guidelines and/or availability of brochures in the clinic that detail the type of information that can help patients better sleuth their family history can be an effective way to disseminate the message. While genetic testing is available and can provide an "answer," what's

much more important is the "question" being asked, the counseling done before making a recommendation for testing and what to do with the information, positive or negative. ■

# Oral Contraceptives and Breast Cancer in Young Women

ABSTRACT & COMMENTARY

***By Leon Speroff, MD, Editor***

***Synopsis:*** *American case-control study finds no increase in premenopausal lobular breast cancer associated with oral contraceptive use.*

**Source:** Nyante SJ, et al. The association between oral contraceptive use and lobular and ductal breast cancer in young women. *Int J Cancer.* 2007;epub Oct 23, 2007.

A TEAM OF EPIDEMIOLOGISTS FROM SEVERAL INSTITUTIONS in the US performed a case-control study of the association between oral contraceptive use and lobular and ductal breast cancer occurring in young women (under age 44).[1] Cases included 100 lobular cancers and 1164 ductal cancers. The results were as follows:

| | Lobular Ca | Ductal Ca |
|---|---|---|
| Ever use of OCs | 1.10 (0.68-1.78) | 1.21 (1.01-1.45) |

The authors concluded that the use of oral contraceptives has no meaningful effects on breast cancer according to histologic subtype.

■ **COMMENTARY**

Lobular cancer (15% of all breast cancers) has been increasing in the US in recent years, prompting these investigators to ask whether this reflects exposure to exogenous hormones. According to their data, the answer is no. This is very reassuring because it is well-recognized that lobular cancer is more hormonally sensitive than ductal breast cancer.

It is disappointing that the article gives a biased point of view, stating that "it has been consistently shown that oral contraceptive use is associated with an increased risk of breast cancer in young women." To support that claim, they site 14 studies with only one in opposition. Two of the 14 are the same study, and one is the collaborative reanalysis of previous studies, published in 1996. That leaves 11 studies. The 11 studies date from 1981 to 1991, thus reflecting old, high-dose oral contraceptives no longer used. The negative study was reported in 2006 with data derived from users of low-dose oral contraceptives.

Most importantly, the authors ignore other recent studies that reflect low-dose oral contraceptives. In the largest case-control study by far, the Centers for Disease Control and Prevention found no increase in risk, even with initiation at a young age and with increasing duration of use.[2] A large study using cases from 3 different countries focused on premenopausal breast cancer and could not detect an increase in risk in current oral contraceptive users.[3]

Finally, all of the studies that have reported small increases in premenopausal breast cancer have been unable to avoid being confounded by a very likely possibility: early and recent use of oral contraceptives may affect the growth of a preexisting malignancy. This is supported by the fact that those studies with positive findings find an increase limited to current and recent use, and the increase has been largely localized disease (in many studies, only localized disease).

Another consideration is the fact that most premenopausal breast cancers are estrogen-receptor negative. Hormone-responsive breast cancers in premenopausal women are more likely to be lobular cancers. For this reason, this negative report on lobular cancer gives more reason to believe that low-dose oral contraceptives have little, if any, effect on breast cancer risk.

I think the following conclusions are appropriate: Even if there is a small increase in premenopausal breast cancer associated with oral contraceptives, this would be a very small number of cases because most cases of breast cancer occur after age 40. Well-done and large case-control studies of modern low-dose oral contraceptives have been consistently negative and reassuring. Older positive studies cannot escape the possibility of detection/surveillance bias because of an effect on preexisting tumors. ■

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# CME Questions

**33. The following statements are true regarding oral contraceptive use and the risk of breast cancer except:**

a. Some studies find a small increase in pre-menopausal breast cancer in OC users.
b. Those studies finding an increase report similar results in current and past users.
c. Lobular breast cancer is usually hormonally sensitive.
d. Ductal cancer is the most common breast cancer.

**34. The following statements are true regarding tamoxifen prevention of breast cancer except:**

a. The overall balance of the risk-benefit ratio with tamoxifen prevention is clearly and significantly positive.
b. Tamoxifen has no impact on estrogen receptor-negative breast cancers.
c. Tamoxifen exposure may increase the incidence of estrogen-receptor negative tumors.
d. The major tamoxifen side effects are due to its estrogenic agonistic actions on certain target tissues.

**35. The following statements are true regarding bisphosphonate treatment and osteomyelitis:**

a. This bone side effect is greater with increasing dosage.
b. Dosage can be regulated by careful monitoring of amount of administered drug.
c. Not all cases have been in patients with cancer.
d. Dental evaluation should be considered before treatment.

# CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

**36. Which of the following is not reflective of the study results?**

a. The Cesarean section rate was diminished 15-fold in those in whom the rotations were successful.
b. Virtually all of the patients had epidurals.
c. Only 20% of rotations were done before full dilatation
d. The Apgar scores were lower in those having a rotation.

**37. Manual rotation can:**

a. potentially diminish maternal morbidity
b. decrease fetal morbidity
c. be successful even after 3 attempts
d. eliminate the need for epidural

**38. Which of the following carcinomas are NOT associated with the spectrum of primary sites associated with the Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome?**

a. carcinoma of the small bowel
b. carcinoma of the ureter
c. carcinoma of the pancreas
d. carcinoma of the endometrium
e. all are encompassed in the spectrum of HNPCC

**Answers:** 33 (b); 34 (a); 35 (b); 36 (d); 37 (a); 38 (e)



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# Adult Immunization Guidelines from CDC Released

***In this issue:*** *Updated Immunization Guidelines from the CDC; Do antivirals have a role in the treatment of Bell's palsy? Topiramate is a promising treatment for alcohol dependence; and FDA Actions.*

The *Annals of Internal Medicine* has published updated Adult Immunization Guidelines from the CDC as an early release article on their website dated October 18. Full guideline will be available in the November 20 print edition. The guideline has several important changes and updates.

The new herpes zoster vaccine is added to the guideline this year. The vaccine should be given routinely to all immunocompetent adults age 60 and older. It is not recommended for immunocompromised adults as it is a live attenuated virus. The vaccine is given once in a lifetime, and does not require a booster.

The new human papilloma virus has also been added. The vaccine protects against 4 types of HPV, which causes 90% of genital warts and 70% of cervical cancers. It is recommended for women aged 11 to 26 years. It requires three doses given at zero, 2 and 6 months. It should not be given to pregnant women.

The new pertussis vaccine is coupled with diphtheria and tetanus to form Tdap (Adacel- Sanofi Pasteur). This is a 1-time, 1-dose vaccine that should be given to all adults age 64 or younger when they are scheduled for their next tetanus (Td) booster. Tetanus boosters should be given every 10 years, but the interval may be shortened to as little as two years for high-risk patients including postpartum women, close contact of infants younger than 12 months of age, and all healthcare workers with direct patient contact. It has not been tested in adults age 65 or older. This vaccine is different from the previously approved Tdap for adolescents aged 10 to 19 (Boostrix-GlaxoSmithKline).

There are now 15 indications for influenza vaccine. New indications include those who have difficultly handling respiratory secretions or have increased risk of aspiration. All women who are pregnant or will be pregnant during the flu season should be vaccinated. All healthcare workers should be vaccinated unless they have strong contraindications.

Hepatitis B vaccine recommendations have changed, and the vaccine is now recommended for all sexually active adults who are not in a long-term mutually monogamous relationship.

Because of several recent large-scale mumps outbreaks in this country, a mumps vaccine booster is now recommended for specific age groups, especially adults who work in healthcare settings. The standard is to give MMR, even if immunity exists for one or more of the components of MMR.

The pneumococcal vaccine recommendations remain the same. The vaccine should be given at age 65 unless the patient has specific risk factors, in which case it should be given to those younger than 65. A small subgroup of patients should be given a second booster. If the vaccine was initi-

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ated under age 65 for high-risk patients, a booster should be given at age 65 or five years after the initial vaccine. If the vaccine was initiated over age 65, a booster should only be given to immunocompromised patients after five years. The vaccine should not be given every five years (a common misconception). In fact, no one should receive more than two doses under any circumstances. There is even some evidence that more than two doses may be harmful and could potentially attenuate the immune response.

## Antivirals and Bell's Palsy?

Do antivirals have a role in the treatment of Bell's palsy? This question has been debated for decades, with several small studies indicating a relationship between herpes simplex infections and facial paralysis. Despite this, treatment with acyclovir or valacyclovir has not been proven to be effective in treating Bell's palsy. Regardless, antivirals are frequently prescribed along with oral steroids. A new study confirms that steroids are useful, but antivirals are not. Nearly 500 patients with new onset of Bell's palsy were randomized to 10 days of treatment with prednisolone, acyclovir, both agents, or placebo. The primary outcome was recovery of facial function. At three months, the proportion to patients who had recovered facial function were 83.0% in the prednisolone group compared with 63.6% among patients who did not receive prednisolone ($P < 0.001$) and 71.2% in the acyclovir group as compared to 75.7% among patients who did not receive acyclovir (adjusted $P = 0.50$). After nine months, recovery was 94.4% for prednisolone and 81.6% for no prednisolone ($P < 0.001$) and 85.4% for acyclovir and 90.8% for no acyclovir (adjusted P = 0.10). For patients treated with both drugs, recovery was 79.7% at 3 months ($P < 0.001$) and 92.7% at nine months ($P < 0.001$). There were no serious adverse effects in either group. The authors conclude that early treatment with prednisolone significantly improves the chance of complete recovery, while there's no evidence of benefit with acyclovir alone or in combination with the steroid (*NEJM*. 2007; 357:1598-1607).

## Topiramate Promising for Alcohol Treatment

Topiramate is a promising treatment for alcohol dependence according to a new study. The drug was shown to be effective in this role in a small study published in 2003. This new, larger multisite 14 week double-blind, randomized, placebo controlled trial enrolled 371 men and women age 18 to 65 years who were diagnosed with alcohol dependence. Up to 300 mg per day of topiramate was given to 183 participants while 188 were treated with placebo. Both groups were enrolled in a weekly compliance enhancement intervention program. The primary end point was self-reported percentage of heavy drinking days, while secondary outcomes included other self-reported drinking measures along with laboratory measures of alcohol consumption. Topiramate was more efficacious than placebo at reducing percentage of heavy drinking days from baseline to 14 weeks (mean difference 8.44%; 95% CI, 3.07%-13 .80%; $P = .002$). Topiramate also reduced all of the drinking outcomes ($P <.001$ for all comparisons). Adverse events were more common with topiramate, including paresthesia (which occurred in over 50% of those on the drug), taste perversion, anorexia and difficulty with concentration. In general, however, the drug was safe and consistently efficacious for treating alcohol dependence (*JAMA*. 2007;298:1641-1651). An accompanying editorial points out that the benefits of topiramate were still increasing at the end of the study, indicating the longer treatment may be more effective (*JAMA*. 2007;298:1691-1692).

## FDA Actions

The FDA has announced new warnings on phosphodiesterase type 5 inhibitors regarding hearing loss. The drugs include sildenafil (Viagra, Revatio), tadalafil (Cialis) and vardenafil (Levitra). The agency has received 29 cases of sudden hearing loss associated with use of the drugs dating back to 1996. Most cases were unilateral and temporary.

Modafinil (Provigil) has also been the subject of new warnings including serous rashes and psychiatric symptoms. The drug, which is used for narcolepsy, obstructive sleep apnea, shiftwork disorder, and multiple sclerosis, has been associated with severe rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. The FDA suggested caution should be exercised when modafinil is given to patients with a history of psychosis, depression, or mania.

An FDA advisory panel has recommended restricting childhood cold medications to children over the age of six years. They also recommend strong limits on marketing these products for younger children. This follows a voluntary withdrawal from the market of infant cough and cold medications by most manufacturers of these products. Voluntary withdrawal involves medications used in children younger than two years. The drugs that contain decongestants and antihistamines have been associated with more than one hundred deaths since 1969. ■