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Long-Acting Reversible Contraception

ABSTRACT & COMMENTARY

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports no financial relationships relevant to this field of study.

Synopsis: *In this large prospective cohort study, women using the pill, patch, or ring were 22 times more likely to experience a contraceptive failure than those using the IUD, subdermal implant, and DMPA injection.*

Source: Winner B, et al. Effectiveness of long-acting reversible contraception. *N Engl J Med* 2012;366:1998-2007.

The authors performed a prospective cohort study, the Contraceptive CHOICE Project, in which women in the St. Louis, Missouri, region received a reversible contraceptive method of their choice for up to 3 years at no cost. The participants were read a standardized counseling script that stated that IUDs and the subdermal implant were the most effective methods of contraception. The women then chose their desired method and were followed prospectively so that contraception continuation and pregnancies could be ascertained. The first 7486 women who used an IUD, implant, depot medroxyprogesterone acetate (DMPA) injection, pills, patch, or ring were analyzed in this report, where the primary outcome was contraceptive failure. Contraceptive-method failure was defined as a pregnancy that occurred when the contraceptive method was actually being used. The women were divided into a long-acting reversible contraception (IUDs and implant) group, a DMPA group, and a pill/patch/ring (PPR) group.

Winner and her colleagues found 156 unintended pregnancies that were attributed to IUD, implant, DMPA, pill, patch, or ring failure. The failure rates for the PPR group were 4.8%, 7.8%, and 9.4% for years

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1, 2, and 3, respectively. The corresponding rates for the long-acting reversible contraception (LARC) group were 0.3%, 0.6%, and 0.9% ($P < 0.001$) and the DMPA group was similar (0.1%, 0.7%, and 0.7% for years 1, 2, and 3, respectively). The risk of unintended pregnancy for the PPR group remained higher than the LARC group after controlling for age, educational level, and number of previous unintended pregnancies (hazard ratio 21.8, 95% confidence interval 13.7 to 34.9). The authors also determined that women younger than 21 years of age in the PPR group had almost twice the risk of unintended pregnancy as older women using these methods after controlling for educational level and previous unintended pregnancy (hazard ratio 1.9, 95% CI 1.2 to 2.8). Age did not impact contraceptive failure in the DMPA and LARC group.

■ COMMENTARY

The authors conducted this study to provide reliable prospective data on contraceptive failure rates for different methods of reversible contraception. Previous estimates of contraceptive failure rates had been based on retrospective studies. Given that the pill, patch, and ring are user-dependent compared to the IUD and implant, it is not surprising that more contraceptive failures occurred in the PPR group. Having to remember to use a medication daily, weekly, or even monthly can be challenging, especially for the adolescents. Interestingly, the DMPA injection group did not differ from the LARC group in this study. This is likely because the authors categorized a pregnancy in DMPA users as a true contraceptive failure only in those compliant with injections. Therefore, this represents "perfect" use of DMPA rather than "typical" use where women might not adhere to injection schedules and failure rates will be higher.

In the United States, the unintended pregnancy rate currently stands at 49% and is a major public health problem.[1] The most common reversible methods of contraception used in the United States are oral contraception and male condoms.[2] As noted above, condoms and oral contraceptives are dependent on user adherence and therefore have higher failure rates among typical users. In contrast, LARC, due to its high efficacy and continuation rates, is considered in the top tier of contraceptive efficacy, as this study confirms. Rather than presenting all contraceptive options as equal alternatives, we should now be offering LARC as first-line contraceptive agents for women.[3] The Contraceptive CHOICE Project investigators have previously reported continuation rates at 12 months of 88% for the levonorgestrel IUD, 84% for the copper IUD, and 83% for the subdermal implant.[4] Satisfaction rates were also higher for LARC methods compared to other methods of contraception, such as oral contraceptives and DMPA. Unfortunately, as of 2008 in the United States, only 5.5% of women practicing contraception used IUDs, and implant users were even fewer.[2] The advantages of LARC also include few contraindications and cost-effectiveness. Current guidelines for LARC use have expanded IUD eligibility to nulliparous and adolescent women.[5] Therefore, almost all women are candidates for these methods and we need to do a better job of making LARC more accessible.

Of course, sometimes the question is how to convince our patients to try IUDs or the subdermal implant when they may fear side effects or having something "foreign" in their body. This study showed that with standardized counseling 5781 (77%) of 7486 women chose LARC methods. Adolescents in this project also had high uptake of both IUDs and implants.[6] So what does their counseling script say?

One of our objectives is to be sure women are aware of all contraceptive options, especially the most effective, reversible, long-acting methods. These methods include intrauterine contraception (the IUD) and the subdermal implant called Implanon. IUDs are completely reversible contraceptive methods placed in the uterus. There are two types of IUD. One is hormonal and lasts up to 5 years (Mirena). The other, ParaGard, is nonhormonal, contains copper, and can last up to 10 years. Both may be removed at any time if you wish to become pregnant or want to switch to a new method. They are very safe and have the highest satisfaction and continuation rates of any contraceptive method. Implanon is a single flexible plastic rod placed under the skin of your upper arm. It is hormonal and lasts up to 3 years. It may also be removed if you wish to become pregnant or

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Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

would like to switch to a different method. Do you have any questions about these methods?

I try to use this counseling message with my patients and also emphasize the fact that they should at least try an IUD or implant. If they don't like it, then it can be removed, but they will never know if they don't try. ■

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PARP Inhibitor Maintenance SCORES in Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationships relevant to this field of study.

Synopsis: *Olaparib, a PARP inhibitor, significantly improved progression-free survival among platinum-sensitive recurrent high-grade ovarian cancer patients when administered as a maintenance agent. Patients were not preselected for BRCA1 or BRCA2 mutation carrier status, highlighting the role for this class of agent in tumors with homologous recombination deficiency.*

Source: Ledermann J, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012;366:1382-1392.

POLY(ADENOSINE DIPHOSPHATE [ADP]-RIBOSE) POLYMERASE (PARP) is an enzyme participating in low-fidelity DNA repair of single strand breaks. Pharmacologic inhibition of PARP has shown to be effective in tumors lacking homologous recombination, such as those harboring silencing mutations of BRCA1 and 2. However, clinical activity also has been demonstrated in patients without these mutations. These observations led to a randomized, double-blind, Phase 2 trial of maintenance olaparib, an oral PARP inhibitor, vs placebo in women with platinum-sensitive, high-grade serous ovarian cancer who had achieved at least a partial response to their antecedent platinum-based chemotherapy. Patients were not required to have germline mutation in BRCA1 or 2. The primary endpoint was progression-free survival (PFS). Olaparib (400 mg BID orally) was administered until disease progression or unacceptable toxicity. Three hundred twenty-six patients were registered and 265 met eligibility criteria. PFS was significantly longer with olaparib than with placebo (median, 8.4 months vs 4.8 months; hazard ratio [HR] 0.35; 95% confidence interval 0.25 to 0.49; $P < 0.001$). The effect was consistent across all subgroups, including BRCA status, of which approximately 22% in both groups carried germline BRCA1 or 2 mutation and approximately 14% in both groups were known wild type; the remainder were unknown. The median number of prior platinum regimens and prior chemotherapy regimens were 2 and 3, respectively, although some patients had substantially more prior therapy. Adverse events more commonly reported in the olaparib arm were nausea (68% vs 35%), fatigue (49% vs 38%), vomiting (32% vs 14%), and anemia (17% vs 5%); however, the majority of adverse events were grade 1 or 2. Although the data are immature (just 38% of events recorded), no benefit was seen on overall survival. The study confirmed activity of olaparib in high-grade, serous, relapsed, platinum-sensitive ovarian cancer. No new safety signals were detected in this largest cohort of treated patients.

■ COMMENTARY

"Individualized therapy" is an easy concept to comprehend, but an extremely difficult one to enact for patients with ovarian cancer. While making informed decisions about specific therapy through some interrogation of a patient's tumor should translate to better outcomes, our ability to find the biological "Achilles heel" at any one time — or even more challenging, over time — is tragically limited. This is due in part to insensitivity of our methods to identify key vulnerabilities, the limitation of known targets, the inability to hit targets-of-interest pharmacologically, the lack of reproducible methods to assess tumor biology in a serial manner or in response to treatment, the spatial heterogeneity of the oncogenic process (primary vs metastases, tumor vs stroma, central tumor vs periphery, etc.), and the

genomic instability of ovarian cancer in general.[1] However, despite these limitations, patients with tumors deficient in homologous recombination processes (HRD) are a genetic "set-up" for therapy exploiting other compensatory DNA repair mechanisms for survival, such as PARP. Either event (HRD or inhibition of PARP) is not universally lethal; however, PARP inhibition in the setting of HRD is lethal — a strategy also known as "synthetic lethality."[2]

It has been previously well described that the BRCA genes are important regulators of high-fidelity homologous recombination repair of double-stranded DNA injury. Their functional absence is easiest to see in patients who carry a germline mutation; however, data from the Cancer Genome Atlas (TCGA) have demonstrated that tumors can develop BRCA malfunction either by somatic mutation or via epigenetic silencing through promoter methylation.[3] In addition, several other genes that contribute to homologous recombination repair processes are frequently altered in high-grade serous ovarian cancer, bringing the potential audience for this individualized therapy (PARP inhibitors) to near 50%.

The current study tested this hypothesis by using clinicopathologic features of HRD: high-grade serous ovarian cancer and platinum sensitivity. While these are crude methods to identify a potential population likely to individually gain from the impact of PARP inhibition, the effect from treatment was dramatic! The HR for PFS is among the lowest ever recorded in an ovarian cancer clinical trial with any therapy. In this study, olaparib was used as an agent to maintain the best treatment effect from a prior platinum therapy; about half of the study population had disease when they were randomized, which explains the shorter than expected duration of progression in the placebo group. Nevertheless, a clear benefit was documented and in the confines of no new safety signals. What would further the "individualized" moniker for this therapeutic strategy would be a test to identify those high-grade serous tumors where HRD was present at the time of treatment. Such strategies, like a RAD51 assay, are currently being pursued.[4,5]

The issue as to whether this class of agent has a role in ovarian cancer management and meets the broadest definition of "individualized therapy" is not largely debated; determining a path to regulatory approval is. The focus on treatment programs that improve only overall survival (immature, but not suggested in this study) has severely hampered clinical development, including this specific agent, which, until just recently was tabled for further development. Fortunately, the current trial's results have sparked renewed interest among companies and investigators and new protocols, including chemotherapy combinations and other biological agents (e.g., anti-angiogenesis and PI3K inhibitors), are planned or in motion offering new hope for effective therapy for these patients.[6] ■

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10 Years after the WHI: Should This Study Guide Our Thinking About Menopausal Hormone Therapy?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *The U.S. Preventive Services Task Force updated its systematic review of menopausal hormone therapy. The findings, heavily influenced by the Women's Health Initiative results, do not support the use of hormone replacement therapy to prevent chronic conditions.*

Source: Nelson HD, et al. Menopausal hormone therapy for the primary prevention of chronic conditions: A systematic review to update the U.S. Preventive Services Task Force Recommendations. *Ann Intern Med* 2012 [Epub ahead of print].

To provide guidance to clinicians on the use of hormone replacement therapy, the authors conducted a systematic review of the randomized, placebo-controlled trials of menopausal hormone therapy published in English since 2002 that assessed primary prevention of chronic conditions. They used several databases and reference lists of published papers to find manuscripts that met these criteria. Investigators extracted data on participants, study

design, analysis, follow-up, and results, and the overall quality of each study was rated by two investigators who worked independently and according to established criteria. Of 4524 abstracts identified from searches, 51 full-text articles that included results from nine randomized trials met the inclusion criteria. However, only the Women's Health Initiative (WHI) main and follow-up studies were considered to meet the criteria for inclusion, as they were designed and powered to focus on the outcomes of chronic disease. Therefore, the WHI findings provided the basis for the results and recommendations of the manuscript.

The estrogen plus progestin (E/P) arm of WHI showed reduced fractures (46 fewer per 10,000 woman-years), but increased invasive breast cancer (eight more per 10,000 woman-years), stroke (nine more per 10,000 woman-years), deep venous thrombosis (12 more per 10,000 woman-years), pulmonary embolism (nine more per 10,000 woman-years), lung cancer death (five more per 10,000 woman-years), gallbladder disease (20 more per 10,000 woman-years), dementia (22 more per 10,000 woman-years), and urinary incontinence (872 more per 10,000 woman-years). Estrogen-only therapy reduced fractures (56 fewer per 10,000 woman-years), invasive breast cancer incidence (8 fewer per 10,000 woman-years), and death (two fewer per 10,000 woman-years), but increased stroke (11 more per 10,000 woman-years), deep venous thrombosis (seven more per 10,000 woman-years), gallbladder disease (33 more per 10,000 woman-years), and urinary incontinence (1271 more per 10,000 woman-years). In their review, the authors state that outcomes did not consistently differ by age or comorbid conditions. The U.S. Preventive Services Task Force (USPSTF) recommendations conclude that while both estrogen plus progestin and estrogen only hormone therapy regimens decrease the risk for fractures, both increase the risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence. While estrogen plus progestin also increases the risk for breast cancer and dementia, estrogen alone decreases the risk for breast cancer.

■ COMMENTARY

If these recommendations sound familiar, it is because they are not changed from those published by the USPSTF in 2002 (after the initial combined estrogen plus progestin WHI study) and in 2005 (after the estrogen only WHI study). So much has happened in the last 10 years, but one thing that has not occurred is another large-scale, randomized trial the size of the WHI. With budget cutbacks at the National Institutes of Health, it is very unlikely that we will ever see this study repeated, so we need to live with the limitations and strengths of the study.

Given that the USPSTF focuses on the highest quality of evidence, it is not surprising that the results of a large randomized, controlled trial (RCT) like the WHI influence these recommendations. If we knew nothing else about the biology of hormonal therapy, it would make sense to follow these guidelines. Fortunately, considerable progress over the last 10 years has helped us place the WHI in perspective.

Without considering this background, the simple repetition of the key findings of the WHI results becomes misleading. This is a particular problem because the opinions of the USPSTF are so influential for our primary care colleagues and for policy makers. The present USPSTF report regurgitates the main findings without providing any real recommendations. On a positive side, the paper reports the attributable risk (of benefits and adverse events) rather than relative risks. However, the conclusions offered simply replay these findings without providing any context as to which women might be at greater or lesser risk, and whether a health benefit might outweigh a particular risk for an individual woman. There is no clear recommendation for postmenopausal women to either use therapy or avoid it. What does it mean that estrogen-only therapy is associated with a reduction in breast cancer risk and overall mortality? So much for guidance.

Our current understanding of hormone replacement therapy (HRT) is that thrombosis is the principle risk, not breast cancer.[1] Thrombosis is related to estrogen-induced changes in hepatic globulins. Current research supports the use of non-oral routes of estrogens, and the use of estradiol rather than ethinyl estradiol to avoid the first pass effect of oral therapy on the liver.[2] I recommend estradiol in a patch, gel, or vaginal ring to my patients and measure estradiol levels to ensure that they are in the 40-100 pg/mL range. Since WHI evaluated only oral conjugated estrogens, it provides no guidance on this important question or route of therapy. Data from the ESTHER study showed no increase in the risk of venous thrombosis in users of transdermal estradiol compared to non-users, but an increase in risk in women using oral products.[3] Although not an RCT, this evidence is compelling and supports that avoiding the first pass effect might be beneficial.

We also know that timing of initiation of therapy matters. Contrary to the discussion of the present USPSTF report that repeated that the main effects of WHI applied to all subgroups, the follow-up reanalysis of the E/P treatment group actually documented a nonsignificant trend toward protection (hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.5-1.5) in women less than 10 years postmenopausal in contrast with the elevated risk (HR 1.71; 95% CI 1.1-2.5) observed in women starting therapy more than 20 years after menopause.[4] The general health and cardiovascular risk factors of an individual woman should be taken into account during the discussion regarding initiation of HRT.

What about breast cancer? The results of the combined

E/P and estrogen only WHI studies differ in several clinically important outcomes. The trend toward a reduction in risk of invasive breast cancer in the estrogen-only arm has persisted in the most recent analysis of results from this study.[5] This is in marked contrast to the results seen with E/P, so medroxyprogesterone acetate must have a negative impact on breast health. The safest choice for systemic progestogen therapy is probably oral micronized progesterone, but we still don't know enough about dose to guarantee endometrial protection.

So the main reason to know about this study is so that you can ignore it. There is nothing new in this paper, and you should continue to provide a balanced discussion of the potential benefits and risks of postmenopausal hormone therapy. ■

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Antenatal Steroids and Fetal Lung Maturity

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships relevant to this field of study.

Synopsis: *A recent study suggests that infants between 34-39 weeks gestation with immature amniotic fluid lung profiles who are managed expectantly have lower rates of adverse neonatal respiratory outcomes as well as lower rates of overall morbities when compared to infants that are delivered after a course of steroids.*

Source: Kamath-Rayne B, et al. Antenatal steroids for treatment of fetal lung immaturity after 34 weeks of gestation: An evaluation of neonatal outcomes. *Obstet Gynecol* 2012;119:909-916.

Apropos of the recent emphasis on discouraging elective deliveries prior to 39 weeks,[1] a group from Cincinnati embarked on a study to determine whether steroids had any neonatal benefit in patients delivering between 34 and 39 weeks who had immature amniotic fluid lung profiles.[2] The authors reviewed the delivery records between 2005 and 2011 from the busiest hospital in Ohio. They found 982 patients who were between 34 and 39 weeks at the time of their amniocenteses. After applying exclusion criteria (which included previous administration of steroids, IUGR, multiple pregnancies, etc.), they were left with 487 patients who had either:

1. A full dose of betamethasone or dexamethasone, given after immature lung profiles (n = 102),
2. Expectant management after immature results (n = 76), or
3. Mature amniotic fluid lung profiles (n = 184).

A variety of respiratory outcomes and neonatal morbidities were assessed that included the necessity for oxygen supplementation, mechanical ventilation, and surfactant administration. In addition, the authors recorded any hypoglycemia requiring IV infusion, the need for antibiotics, or a requirement for phototherapy for hyperbilirubinemia. Most importantly, they tried to rule out potentially confounding maternal factors such as diabetes, preeclampsia, oligohydramnios, premature rupture of membranes, and other pregnancy complications.

Some of the results were expected. For example, the greatest composite respiratory and neonatal morbidities were higher in the late preterm (34 to 36 6/7 weeks) vs the early term (37 to 38 6/7 weeks) groups. Also, the expectant management group had a longer interval between delivery (10.9 days) vs those with mature lung profiles (1.7 days) and the steroid group (3.5 days post-completion of the steroid course).

The most common reasons for an amniocentesis in this entire study population were a prior cesarean section with a classical incision (15.8%), oligohydramnios or polyhydramnios (14.9%), prior fetal death or abruption (9.9%), or diabetes (9.7%).

The outcome data showed the mature amniocentesis group to have the lowest rates of combined respiratory (3.3%) and overall neonatal morbidities (14%). There was a significant difference in these two dependent variables between the steroid group (9.8% and 26.5%) vs the expectant management group (1.3% and 10.5%), respective-

ly. The authors pointed out that those infants born after expectant management, rather than being delivered after steroids, not only gained an average of 7.5 days more in utero, but also had a 40% reduction in composite neonatal morbidity and a 90% reduction in composite adverse respiratory outcome. Specifically, rates were higher for hypoglycemia, suspected sepsis, need for antibiotics, and prolonged oxygen supplementation in the steroid group.

■ COMMENTARY

The obvious flaw in the study was that it was not a randomized trial. The reason that the infants did less well in the steroid group could have been that they were perceived clinically to be in greater need for early delivery — e.g., a loaded deck. For example, this group had a lower average birth weight and higher rate of premature rupture of membranes. Realizing this problem, the authors tried to adjust for variables that might influence the provider's desire to pull the trigger. Nevertheless, despite this possible bias, one cannot exclude the possibility that steroids simply were not protective against respiratory distress syndrome (RDS) and might have given the provider a false sense of security that delivery in the late preterm period could be done safely. It is even possible that the steroids might have been at least partially responsible for the neonatal hypoglycemia and sepsis through its metabolic and anti-inflammatory effects, respectively.

A meta-analysis of early randomized clinical trials suggested that the benefits of steroids seemed to stop at 34 weeks,[3] and, although one study has shown a maturing of weekly amniotic fluid lung indices when steroids were given between 34 and 37 weeks,[4] a recent randomized trial showed no difference in RDS when steroids were given, vs controls, during this period in gestation.[5] This is in contradiction to definite benefits of steroids that have been well demonstrated through the years of their use before 34 weeks for prevention of RDS.[3,6]

Despite the Cincinnati study's warts, the data suggest that if the clinical situation is not deteriorating, the option of watching and waiting in the face of an immature amniotic fluid lung profile at 34 through 38 weeks is preferable to giving steroids followed by delivery. ■

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Patient Attitudes Toward Treatments for Overactive Bladder

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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Dr. Ling reports no financial relationships relevant to this field of study.

Synopsis: *Women with overactive bladder hold differing views of their treatment options in light of the severity of their symptoms as well as the risks/benefits of the modality.*

Source: Wu JM, et al. Patient preferences for different severities of and treatments for overactive bladder. *Female Pelvic Med Reconstr Surg* 2011;17:184-189.

Researchers from Duke University and the University of California, San Francisco enrolled 40 patients with symptoms of overactive bladder (OAB), i.e., urgency, frequency, and/or urge incontinence, and 40 patients with no history of OAB symptoms. The women's view of symptoms and treatments were measured with a utility score.

A utility is defined as "…a quantitative measure of the value that an individual assigns to a specific health outcome." Scores range from 0 to 1.0 where 0 represents death and 1.0 is perfect health. Utilities were measured for four levels of OAB severity as well as three urge incontinence treatments. Significant side effects and/or complications were measured as well. Three treatments/complications were assessed and were defined as the following: 1) anticholinergic agents without side effects or with constipation/dry mouth; 2) botulinum toxin injection

with urinary retention; and 3) sacral neuromodulation with no complications or with subsequent irritation in the lower extremeties or vagina.

Each subject was asked to rate on a scale from 0 to 100 how she would feel about living with each set of health outcomes. The rating was converted to a score between 0 and 1.0, i.e., a rating of 93 became a utility score of .93. Each proposed clinical scenario was described in great detail. By having richer descriptions, there is less room for ambiguity in the subject's response. Subjects also were allowed to adjust their rankings in relation to their answers to all other responses that they had given. This allowed the subject to change earlier responses in light of additional situations described later in the instrument, thereby allowing her to respond to each item within the context of all the scenarios described. The highest scores (both median and mean) were for mild urge incontinence (0.92 and 0.82, respectively). As the severity of urgency increased, scores decreased. A condition of frequency/urgency without incontinence scored between mild and moderate incontinence.

As for treatments for OAB, the least invasive (oral anticholinergics) with no side effects scored the highest (0.93 and 0.84). The lowest scores assigned to treatment were botulinum toxin complicated by urinary retention (0.75 and 0.64).

■ COMMENTARY

Although the concept of "utility" may be new to the reader, it is one that makes both clinical and common sense. Future studies may emphasize the importance of utility scores as newer treatments are studied. The utility score considers quality of life, a concept that many can appreciate but is difficult to measure. Understanding how a patient compares the effects of a chronic health condition vs possible complications of treatment for that condition provides insight into how significant symptoms and treatment are on a patient's lifestyle.

In this article, for example, the authors point out that low utility score of moderate urge incontinence (0.85) and severe urge incontinence (0.73) show that this condition has a "profound" effect on quality of life. For comparison, the following utilities are offered: blindness in one eye (0.93), asthma with dyspnea (0.89), moderate chest pain (0.83), and mild dementia (0.65). Findings that more severe OAB symptoms are assigned a lower utility score and that any treatment is given a higher utility than the same treatment with a complication show that this measure of utility makes clinical sense.

More importantly, in any given patient that we see in the office each day, we commonly provide choices that simulate this very process. "Mrs. Jones, is the pain bad enough that you would be willing to undergo a surgical procedure such as laparoscopy with its potential complications?" The same implied question applies to any medical or surgical therapy that is offered to a patient. Certainly the likelihood of a specific complication also will color the patient's response, since the utility is a description that presumes that the complication did occur.

Beyond the general concept of utility, the specific findings of the study should lead the clinician back to the important theme of OAB and its effect on quality of life. OAB should not be viewed as merely a nuisance, as utility of both moderate and severe urge incontinence would indicate. Since utility of anticholinergics without side effects scored higher than botulinum toxin without complications, which, in turn, scored higher than sacromodulation without side effects, it would appear that those treatments might logically be offered to patients in that order.

The reader should not be surprised to see the use of "utility" a lot more in our literature in the years to come. Remember, you heard it first here. ■

CME Questions

1. **Women younger than 21 years of age were found to have higher contraceptive failure rates with which of the following methods?**
   a. IUDs
   b. Implants
   c. Depot medroxyprogesterone acetate (DMPA)
   d. Pill, patch, or ring

2. **Which of the following is true regarding the trial of olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer?**
   a. Overall survival was the primary endpoint.
   b. Subgroup analysis suggested that olaparib was effective only among BRCA mutation carriers.
   c. Patients treated with olaparib have more toxicity compared with control therapy.
   d. There was no restriction for histology as eligibility.

3. **What was the most common adverse event in both the estrogen/progestin and estrogen only WHI studies?**
   a. Urinary incontinence
   b. Heart attack
   c. Stroke
   d. Venous thrombosis

4. **Data suggest that steroids followed by delivery prior to 39 weeks of gestation is preferable to watching and waiting between 34 and 39 weeks in the face of an immature lung profile.**
   a. True
   b. False

In Future Issues:

Endometriosis and Cancer

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.*

FDA Approves First New Anti-Obesity Drug in Years

In this issue: Lorcaserin for weight loss; statins and fatigue; treatment-resistant gonorrhea; hydrocodone classification changes; USPSTF recommendations; and FDA actions.

Magic bullet for weight management?

The FDA has approved lorcaserin, the first new weight loss medication in more than a decade. The drug is approved for chronic weight management in adults with a body mass index of 30 or greater, or 27 or greater in those with weight-related conditions such as high blood pressure, type 2 diabetes, or hypercholesterolemia. Lorcaserin works by activating the serotonin 2C receptor in the brain, which promotes satiety. Approval was based on the results of three randomized, placebo-controlled trials of nearly 8000 obese and overweight patients with and without type 2 diabetes. All participants received lifestyle modification and reduced-calorie diets as well as exercise counseling. Lorcaserin was associated with an average weight loss of 3-3.7% compared to placebo over 1 year. Those with type 2 diabetes experienced favorable changes in glycemic control. There is no evidence of valvulopathy associated with the drug; although serotonin syndrome is a concern, especially when the locaserin is taken with an SSRI or some migraine drugs. The most common side effects include headache, dizziness, fatigue, nausea, dry mouth, and constipation as well as hypoglycemia in diabetic patients. Lorcaserin will be marketed by Arena Pharmaceuticals as Belviq. ■

Do statins cause fatigue?

Statins may be associated with fatigue and exertional intolerance, according to a small study from UC San Diego. Researchers randomized just over 1000 patients (692 men and 324 women) to simvastatin 20 mg (lipophilic statin), pravastatin 40 mg (hydrophilic statin), or placebo for 6 months. The outcomes were self-ratings of change in baseline in "energy" and "fatigue with exertion." Statin users were more likely to report worsening energy and fatigue compared to placebo ($P = 0.002$) Fatigue and exertional intolerance was worse with simvastatin compared to pravastatin (simvastatin, $P = 0.03$; pravastatin, $P = 0.01$). Women were more severely affected than men. The authors acknowledge that these findings are based on small numbers and findings are provisional. However, they also state that "this is the first randomized evidence of affirming unfavorable statin effects on energy and exertional fatigue." They further suggest that these effects "germane to quality of life, merit consideration when prescribing or contemplating use of statins, particularly in groups without expected morbidity/mortality benefit." (*Arch Intern Med* published online June 11, 2012. doi: 10.1001/archinternmed.2012.2171). The study also raises the potential issue of increased adverse effects of lipophilic statins such as simvastatin. The various risks and benefits of lipophilicity have been debated for years. It is clear that highly lipophilic statins, such as the now removed cerivastatin (Baycol), may have more muscle toxicity, and may have more CNS adverse effects as well. Of currently marketed statins, simvastatin is the most lipophilic, while pravastatin and rosuvastatin are the least. ■

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Call to action for resistant gonorrhea

The World Health Organization (WHO) is calling for urgent action to prevent the spread of "untreatable gonorrhea" around the world. The concern is based on reports from several countries, including Japan, United Kingdom, Australia, France, Sweden, and Norway, of gonorrhea that is resistant to cephalosporin antibiotics — the last remaining treatment option. According to WHO, more than 100 million people are infected with gonorrhea annually, and the world is faced with "dwindling treatment options." WHO is calling for greater vigilance on the correct use of antibiotics and more research into alternative treatment regimens for gonococcal infections. The agency also calls for increased monitoring and reporting of resistant strains as well as better prevention, diagnosis, and control of gonococcal infections. Single-dose treatment to assure adherence is also important as is the treatment of partners. WHO also stresses education and prevention, with special attention to high-risk groups such as sex workers and men who have sex with men. Cephalosporin-resistant gonorrhea has not been reported in the United States yet, but surveillance systems are in place. According to a recent CDC editorial in the *New England Journal of Medicine,* "It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense..." (*N Engl J Med* 2012; 366:485-487). ■

Changes on horizon for hydrocodone drugs

Could Vicodin soon be a Schedule II drug? The answer may be yes depending on congressional action this summer. The U.S. Senate recently passed The FDA Safety and Innovation Act (S 3187) with an amendment to classify all hydrocodone-containing products from Schedule III to Schedule II. The House of Representative's version of the bill did not contain similar language, and the proposal is under consideration for the final bill to be sent to the President for signature later this summer. Meanwhile, lawmakers in New York are moving forward with legislation that would make all hydrocodone-containing drugs Schedule II. If enacted, these laws would categorize hydrocodone containing drugs, such as Vicodin and Norco, in the same group with morphine, oxycodone, and methadone. Schedule II drugs cannot be phoned in, and patients are required to receive a new prescription for each refill. The proposed tightened regulations are in response to the explosion of prescription opioid abuse nationwide. Meanwhile, pharmacy groups, such as the American Pharmacists Association, are opposed to the legislation and are actively lobbying against it, arguing that it is unnecessarily restrictive to patients who legitimately need access to these drugs. ■

Vitamin D and calcium supplements

The U.S. Preventive Services Task Force (USPSTF) has now recommended that vitamin D and calcium supplements above the usual recommended daily allowances are of no benefit to help prevent bone fractures in healthy older women, and may actually cause harm. In a draft recommendation statement issued in early June, the USPSTF concluded that there is insufficient evidence to recommend vitamin D for prevention of cancer or combined vitamin D and calcium for the prevention of fractures in postmenopausal women or men. They further recommend against daily supplementation of more than 400 IU of vitamin D and 1000 mg of calcium carbonate. Older adults who are at risk for falls may continue to take vitamin D (www.uspreventiveserviestaskforce.org/draftrec3.htm). The draft recommendation was issued just after a study was published showing calcium plus vitamin D supplements appear to be associated with lower mortality in older individuals. In a large meta-analysis, patients receiving both calcium and vitamin D had a 9% reduction in mortality (hazard ratio, 0.91; 95% confidence interval, 0.84-0.98), although vitamin D alone did not affect mortality (*J Clin Endocrinol Metab* published online May 17, 2012, doi: 10.1210/jc.2011-3328). ■

FDA actions

The FDA has issued opinions on two oral novel anticoagulants. The agency turned down Janssen's application for approval of rivaroxaban (Xarelto) for the treatment of acute coronary syndrome, at least for now. The FDA did not release the reasons for the decision, but speculation is they want more information from the ATLAS-ACS trial. Rivaroxaban was approved last year for prevention of venous thromboembolism after hip or knee replacement surgery, and also for stroke prevention in patients with non-valvular atrial fibrillation (AF). The FDA also delayed the approval of apixaban (which would represent the third novel oral anticoagulant along with dabigatran and rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular AF. It had been widely speculated that the drug would be approved this spring, especially given that the FDA had granted a priority review for apixaban last November. The delay is similarly due to the need for additional information from the ARISTOTLE trial. Once approved apixaban will be marketed by Bristol-Myers Squibb as Eliquis. ■