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INSIDE

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A New Wrinkle in the Prevention of Preterm Delivery Through Cervical Cerclage

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: *With normal cervical mucus IL-8, cerclage treatment for cervical shortening may reduce the rate of preterm delivery; but with elevated cervical mucus, IL-8 cerclage may be harmful.*

Source: Sakai M, et al. Evaluation of effectiveness of prophylactic cerclage of a short cervix according to interleukin-8 in cervical mucus. *Am J Obstet Gynecol*. 2006;194:14-19.

IN THE JANUARY ISSUE OF THE *American Journal of Obstetrics and Gynecology* an article from Japan appeared that will shed new light on the practice of using cerclage in patients with short cervices. Over a 5-year period 16,508 had transvaginal ultrasound evaluations between 20-24 weeks. A short cervix was defined as a cervical length of less than 25 mm. At the same time every patient in the study also had an assessment of an inflammatory cytokine, interleukin-8 (IL-8) in her cervical mucus.

Two hundred fifty-six patients (1.49%) had short cervices and, based on the attending physicians' preference (but without the IL-8 information), 165 patients had a cerclage procedure either by McDonald technique (133) or a Shirodkar-like procedure (32). The remaining 81 patients were treated conservatively.

Overall, the rates of preterm birth (PTB) in those 246 patients with short cervices having cerclage and those not having the procedure were the same. However, the presence or absence of the positive cervical IL-8 had a major effect on the results. For example, in those with cervical shortening, the positive IL-8 group had a significantly higher rate of PTB than the normal IL-8 group at < 32 weeks (15% vs

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2.4%), < 34 (27.4% vs 6.5%), and < 37 weeks (68.5% vs 38.7%). Also, when comparing those having cerclages with "controls" with short cervices, those with a normal IL-8 concentration had a lower rate of PTB than those without intervention. The most striking finding was that doing a cerclage in the face of a positive IL-8 value resulted in the highest PTB rate before 37 weeks (78%), and a much shorter procedure-to-delivery interval.

COMMENTARY

To stitch or not to stitch? That has been always been the question in a patient who has a past obstetrical history that suggests cervical incompetence. Now that cervical length measurements are often being employed in those at risk for PTB, the picture is certainly no clearer. Individual randomized clinical trials and a recent meta-analysis have not borne out the therapeutic advantage of prophylactic cerclage in those patients with a history suggestive of incompetent cervix or in those with short cervices prior to 24 weeks. Only one study remains that suggests the benefit of performing a cerclage in at-risk patients showing progressive cervical shortening in the mid trimester.[1-4]

The problem is that only a small percentage of PTBs can be chalked up to a true inability of the cervix to contain the pregnancy. Our lack of success in decreasing PTB stems from the heterogeneity of its cause. For example, it is simplistic to think that every patient presenting with painless early dilation of the cervix or mid-trimester cervical shortening has an incompetent cervix. The cervix responds on command to various hormone and cytokine messages and only occasionally does it passively shorten because it is truly structurally "incompetent." This study definitely lends even more credence to exploring an infectious etiology to preterm delivery before attempting to stop it with tocolytics or a cerclage.

Romero and colleagues have written an excellent companion editorial to the above paper in the same journal.[5] He and his group have found that 50% of patients presenting with a clinical story for incompetence cervix will have a documented silent intrauterine infection, and 9% of patients with a short cervix will have a positive amniotic fluid culture. The above study from Japan indicates that non-invasive assessment of cervical inflammation and, indirectly, intrauterine infection through investigation of a cytokine in cervical mucus, may help in excluding patients possibly destined for a cerclage procedure. While showing that doing a cerclage in a patient with a positive IL-8 is certainly not productive, it does suggest that doing it in a patient with a negative IL-8 could be.

Once again, we are reminded that prevention of preterm birth is a complicated process and while making every attempt to keep fetuses in utero is laudable on the surface, in many cases we are interfering with nature's attempt to get them out before infection and/or cytokines have an irreversible effect on the fetal brain and other organs. That said, this study indicates that perhaps in a small select group of patients we should not completely give up on cerclage. ■

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Questions & Comments

Please call **Robert Kimball**, Managing Editor at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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The Gaining Prominence of Chemotherapy in the Adjuvant Treatment of Advanced Endometrial Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *Chemotherapy with doxorubicin-cisplatin significantly improved progression-free and overall survival compared with WAI. Nevertheless, further advances in efficacy and reduction in toxicity are clearly needed.*

Source: Randall M, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2006;24: 36-44.

Advanced stage endometrial cancer represents a significant therapeutic challenge as it encompasses patients with a diverse spectrum of disease and recurrence risk. Currently, most patients are treated following primary surgical extirpation with a modality either directed at tumor residua or to a high-risk locale of recurrence. Either or both radiation therapy and chemotherapy have been used. Both have been considered to be feasible and effective. Randall and colleagues addressed the question as to which was better in a randomized clinical trial of whole abdominal irradiation (WAI) vs combination chemotherapy with cisplatin and doxorubicin. Nearly 400 patients were entered over 8 years. Patients with stage III or IV (≤ 2 cm post-operative residual) disease were eligible. Both groups were well balanced for known prognostic factors including percent of stage III vs IV disease, nodal status, age, and performance status.

Overall, more patients completed WAI than chemotherapy and experienced less systemic toxicity. Treatment-related deaths, however, were similar on both arms. Progression-free and overall survival were significantly improved with chemotherapy relative to WAI. The reduction in the risk for progression for patients treated with chemotherapy was 33% and for overall survival, 31%; both are highly statistically significant. Subgroup analysis demonstrated that the benefit estimates were similar when evaluated by stage (III vs IV). The authors concluded that cisplatin and doxorubicin chemotherapy significantly improved progression-free and overall survival compared to WAI. However, significant modality-related toxicity should prompt investigation of alternative regimens.

COMMENTARY

Endometrial cancer is the most frequently diagnosed gynecologic malignancy in the United States. Fortunately, most patients have organ-confined disease, which is highly curable with surgery with or without adjuvant therapy. However, patients with more advanced disease comprise the majority of disease-related deaths associated with this condition. Strategies to treat these patients have largely been directed to the known disease (eg, node-bearing tissues) or to the likely patterns of recurrence (eg, vaginal cuff or intra-abdominal locations). This has led to a diverse set of treatment recommendations and a diverse set of reported outcomes in uncontrolled clinical trials.[1-3] Another challenge in this setting is the higher representation of high-grade and atypical histologies, such as clear cell and serous, which have a somewhat different natural history. Thus, a review of the literature comprising patients classified as "advanced stage" leaves the reader with a confusing picture of treatment recommendations and expectations.

Traditionally, it has been felt that advanced stage endometrial cancer patients represent a cohort with a significant risk of local and regional disease recurrence. This has been particularly true of patients with known metastatic disease in the abdomen (Stage IV). Those patients with small volume residual disease following surgery have been approached with WAI with significant survival characteristics. Given that patients may recur distantly with similar probabilities, attention has recently turned to the evaluation of systemic chemotherapy. The current trial represents the first such completed trial comparing the modalities head to head. It was somewhat of a surprise that chemotherapy performed as well as it did. Despite being more toxic and less likely to be completed in full, it significantly reduced the risk of disease progression and death by almost one-third. The results held true even in cases where radiation is considered a favored modality

given its long track record of success and the oft-considered chemotherapy-sanctuary of the retroperitoneal lymphatics. To be fair, it is likely that WAI is not the best form of radiotherapy to administer in this setting, particularly in patients with stage III disease or in patients with 2 cm macroscopic residual tumors. Better case selection may have offered a more balanced trial. However, these results have ushered in an intensive investigation portfolio of expanded chemotherapy use and novel treatment packages utilizing radiation and chemotherapy for similarly staged patients. The report represents a significant contribution to the literature and is a tribute to the Gynecologic Oncology Group's investigator's tenacity to complete a difficult trial of divergent methodologies. ■

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Tibolone and Atherosclerosis

ABSTRACT & COMMENTARY

By Leon Speroff, Editor

Synopsis: *Both tibolone and CEE/MPA showed increased progression of common CIMT. Translation of the increased common CIMT progression of the CEE/MPA group into cardiovascular disease risk could not fully explain the observed increased cardiovascular risk as observed in the WHI study.*

Source: Bots ML, et al. The effect of tibolone and continuous combined conjugated equine oestrogens plus medroxyprogesterone acetate on progression of carotid intima-media thickness: the Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) study. *Eur Heart J*. [Epub ahead of print] January 16, 2006.

THE OSTEOPOROSIS PREVENTION AND ARTERIAL Effects of tiboLone (OPAL) study was a 3-year, randomized, double-blind trial in 6 US centers and 5 European centers, treating 866 postmenopausal women with either 2.5 mg tibolone daily, 0.625/2.5 mg daily of conjugated estrogens/medroxyprogesterone acetate, or placebo. The arterial end point of the study was carotid intima-media thickness measured by ultrasonography every 6 months. Overall, 603 women (70%) completed the trial, essentially 200 in each group. The average age of the subjects was 59 with an average of 10 years since menopause. About 47% had previously used hormone therapy. Both the tibolone-treated group and the estrogen/progestin-treated group demonstrated an increase in intima media thickness over the time period of the study, at a rate significantly greater than the placebo group. The authors concluded that both tibolone and estrogen/progestin treatment increased atherosclerosis compared with the placebo group.

■ COMMENTARY

It has been recognized for many years that tibolone lowers HDL cholesterol levels by 20-30%. This has raised concern that treatment with tibolone would have an adverse effect on arterial blood vessels. The OPAL study was designed to address this concern, but its results are disappointing for several reasons.

It is not a given that reducing HDL cholesterol will have an adverse impact, because what really counts is whether cholesterol continues to be removed from cells and metabolized (so-called cholesterol efflux). Studies of cholesterol efflux in monkeys and women indicate that efflux is not impaired despite a tibolone-induced reduction in HDL cholesterol.

Measurement of carotid intima-media thickness is an appropriate end point, because progression of thickness is correlated with risk of vascular disease. The problem therefore lies elsewhere. Why did treatment with estrogen/progestin increase intima-media thickness despite lowering HDL cholesterol, contrary to previous reports, most noteworthy being the EPAT study.[1] Do the results reflect the fact that the study population was relatively older, an average of 10 years away from menopause? For example, the HERS secondary cardiovascular trial of older women found no beneficial effect of estrogen/progestin treatment.[2]

The European women differed from the American women in multiple ways: higher lipids, higher blood pressure levels, more smokers. Hysterectomized women were excluded in the United States, but not in Europe (28% of the study population). In an excellent editorial that accompanies this report, Tom Clarkson reviews the experimental results in his monkey model, indicating that tibolone has neither a beneficial nor an adverse effect on atherosclerosis, a finding that is in keeping with

maintenance of cholesterol efflux despite lower HDL cholesterol levels. Clarkson further emphasizes the different results in the European women compared with the American women. The overall mean results, indeed, indicate a difference comparing both treatment groups to placebo. But in the European women, atherosclerosis, measured by intima-media thickness, improved in the placebo group, making it easy to calculate a significant difference compared to the treated groups! In American women, there were no differences comparing the 3 treatment groups, all demonstrated progression of thickness. Thus the overall conclusion is inordinately influenced by the results in the European women. The investigators could not explain these differences.

Changes in carotid intima-media thickness were compared to the values at baseline. And all three groups of women demonstrated an increase. But this increase was observed at the very first 6-month measurement. From that point on, there was little change. One could interpret the results in the following fashion: the 3 groups differed from each other in some unknown way before treatment, and treatment produced no major changes. The authors could find no explanation for this rapid change, and subsequent leveling off.

Tibolone treatment of postmenopausal women is as effective as estrogen therapy in relieving hot flushes, preventing bone loss, and increasing vaginal lubrication, but it stimulates libido to a greater degree than estrogen. The final target tissue response to tibolone depends on which of its active metabolites predominates in that tissue. Two of the metabolites are estrogenic and predominate in the circulation. The third metabolite is progestogenic and androgenic, and fortunately predominates in the endometrium. Thus tibolone, soon to be on the market in the United States, is an attractive choice for postmenopausal women and clinicians. The results from ongoing clinical trials will document the efficacy and safety of tibolone, especially for fractures and risk of breast cancer. Unfortunately, the OPAL trial did not achieve its goal of providing robust data on cardiovascular effects, due to the older age of the women and the notably different results in American and European women. There continues to be good reason to believe that tibolone will have a neutral effect on the cardiovascular system. ■

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Bladder Injury During Vaginal Hysterectomy After Cesarean Delivery

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: *Cumulative data from 4 studies published between 1980 and 2003 show that the risk of bladder injury during vaginal hysterectomy does not appear to be increased in women who have undergone cesarean delivery.*

Source: Agostini A, et al. Risk of bladder injury during vaginal hysterectomy in women with a previous cesarean section. *J Reprod Med*. 2005;50:940-942.

A MEDLINE SEARCH WAS CONDUCTED FOR COMPARisons of vaginal hysterectomy in patients with/without previous cesarean delivery. As might be anticipated, the studies were heterogeneous. For example, in one study, some cases had laparoscopic assistance. In some studies, patients with prolapse were included. The studies were typically retrospective, the statistical analysis was multivariate in only 1 study, and the total number of patients relatively small (n = 430 with previous cesarean delivery, 1227 without). Due to the size of the population, the authors were unable to address the effect of the number of cesarean deliveries.

The rates of bladder injury were not statistically different (1.86% vs 0.89%). Unfortunately, several key factors could not be analyzed. The presence/absence of previous vaginal delivery could be important, but was not addressed here. Similarly, the size of the uterus and the presence of fibroids would logically be potential predictors of bladder injury. The authors suggest that the indication for the cesarean delivery would potentially impact on the rate of bladder injury. Particularly in patients who were deemed to have an inadequate pelvis at the time of cesarean delivery, the likelihood of limited visualization at the time of hysterectomy is

increased. Also, post-cesarean adhesions may well reduce the uterine mobility.

COMMENTARY

For the gynecologic surgeon, the choice of approach for hysterectomy is a very personal one. For example, the size of the uterus may well exceed an individual surgeon's comfort level for a vaginal approach while well within that of another's. Previous pelvic surgery, and particularly previous delivery, remains a key historical point for many surgeons, and, therefore, their patients. One doesn't have to work very hard to find a gynecologic surgeon who considers previous cesarean delivery to be a relative contraindication to a vaginal hysterectomy due to the risk of bladder injury. Interestingly, many would argue (myself included), that it is easier to dissect a scarred bladder off the cervix vaginally rather than abdominally, if nothing else, because of the ability to visualize the anatomy more closely.

This is not a "right/wrong" decision, but a "better/best" one. Surgeons should not only rely on their experience and clinical acumen, but also the literature in order to make the best decisions for their patients. A previously scarred bladder flap does not necessarily mandate an abdominal approach, only closer attention to how the bladder is advanced. This is why I am not a proponent of teaching younger surgeons to use a sponge-stick to develop a bladder flap, even on patients with no previous scarring of the bladder flap. I much prefer to have them learn sharp dissection so that they can be more facile in cases where the bladder is expected to be scarred.

An article such as this doesn't give us the definitive answer. It should, however, stimulate us to think about how we do certain things, such as decide on a surgical approach for hysterectomy, or incise the vagina in preparation for developing a bladder flap, or advance the bladder as the supportive structures of the vagina are being clamped, cut, and tied. In my own experience:

1. previous cesarean delivery does not necessarily rule out a vaginal approach to hysterectomy;
2. to attempt a vaginal hysterectomy, there should be a wide pubic arch, reasonable mobility of the uterus, a reasonable sized uterus, and no suspected significant adnexal pathology;
3. you don't have to "get in anteriorly" in order to proceed with the vaginal hysterectomy, but you do need to keep advancing the bladder before the next bite;
4. sharp dissection of the bladder flap is a good thing to become comfortable with on uncomplicated cases in anticipation of the scarred bladder flap.

There are certainly other factors which weigh into our decision-making, but I would challenge each of us to keep advancing our surgical expertise and not operate in a certain way just because "that's the way I was taught." ■

Risk-Reducing Surgery in Women with Lynch Syndrome has Merit

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Synopsis: *These findings suggest that prophylactic hysterectomy with bilateral salpingo-oophorectomy is an effective strategy for preventing endometrial and ovarian cancer in women with the Lynch syndrome.*

Source: Schmeler KM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med*. 2006;354:261-269.

THE LYNCH SYNDROME (HEREDITARY NON-POLYPOSIS colorectal cancer) is a cancer susceptibility syndrome highlighted by early age onset of cancers of the colon and rectum, endometrium, ovary, small bowel, ureter and renal pelvis. It is mediated via autosomal dominant transmission of germ-line mutations in DNA-mismatch repair genes. In recent years, it has become recognized that lifetime risk of cancers of the endometrium is similar to that of colon cancer. Since prophylactic surgery in women with BRCA mutations reduces their risk of ovarian and breast cancer, it was hypothesized that similar reductions in endometrial, ovarian and colon cancer may be levied by prophylactic hysterectomy and/or oophorectomy. To test this hypothesis, Schmeler and colleagues performed a case-control retrospective study of 315 women with known germ-line mutations associated with the Lynch syndrome. Approximately 20% had undergone prophylactic hysterectomy (with or without oophorectomy); age-match controls were identified. There were no cases of endometrial, ovarian or primary peritoneal cancer in the group undergoing surgery. Endometrial cancer was identified in 33% of the controls and ovarian cancer in 5% of the controls.

The cumulative risk reduction of these cancers imposed by surgery was 100%. Eighty-eight percent of synchronous or metachronous colon cancers were diagnosed after age 35 supporting the authors recommenda-

tion that such surgery could be performed after childbearing. They also concluded that prophylactic hysterectomy is an effective strategy to reduce the risk of endometrial and ovarian cancers in affected women.

COMMENTARY

The article by Schmeler and colleagues is provocative even though retrospective in nature and subject to the usual biases of ascertainment. The authors essentially report (and somewhat obviously) that prophylactic hysterectomy prevents lifetime occurrence of endometrial cancer and (less obviously) in the presence of oophorectomy nearly significantly reduces the lifetime risk of ovarian cancer. In this study, no cases of gynecologic cancer were diagnosed subsequent to the procedure. This is an important observation as the lifetime risk of endometrial cancer among affected individuals is as high, if not higher, than their risk of colon cancer, for which this syndrome is commonly referred to (hereditary non-polyposis colorectal cancer [HNPCC]). A small number of cases of ovarian cancer limited the statistical inference of hysterectomy and oophorectomy on subsequent primary peritoneal cancer.

In the accompanying editorial to the article, Offit and Kauff point out that over-estimation of the risk-reduction potential may indeed be occurring in this case-control study largely from higher than expected disease density in the controls. The reported incidence was nearly 3 times the previously reported risk in other HNPCC studies. However, a reduction to zero from just about any baseline value needs to be seriously considered in counseling at-risk patients. This is further underscored by the fact that effective screening for the disease processes, namely endometrial and ovarian cancer in those in whom surgery is not performed is limited and not validated. However, since surgery may be associated with morbidity, the careful risk-benefit ratio must be objectively presented.

Ultimately, any risk-reduction surgery should translate into improved survival of the treated cohort. This has been preliminarily demonstrated in one ovarian cancer population-based screening study. However, since endometrial cancers are frequently diagnosed in older women, at early stages, with attendant comorbidities, this may not be overtly obvious. However, the age of onset of cancers identified in women with a germ-line mutation is substantially younger and presents a potential life expectancy within which such an effect may be measured. Subsequent prospective cohort trials, as planned within the Gynecologic Oncology Group will hopefully shed light on this important effect. ■

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How are Fibromyalgia, Depression, and Sexual Dysfunction Related?

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: *Sexual dysfunction, most commonly low libido, is more common in patients with fibromyalgia than in healthy controls.*

Source: Aydin G, et al. Relationship between sexual dysfunction and psychiatric status in premenopausal women with fibromyalgia. *Urology*. 2006;67:156-161.

The authors sought to determine the relationship between psychiatric and sexual status of premenopausal women with fibromyalgia compared to a control group of healthy women. Forty-eight women with fibromyalgia and 38 control patients completed Female Sexual Function Index (FSFI), the State-Trait Anxiety Inventory (STAI), and the Beck Depression Inventory (BDI).

The average BDI was significantly greater in the fibromyalgia patients and the mean FSFI was significantly lower. The incidence of sexual dysfunction was 54% in the study population compared to only 16% in the control group. The most common sexual problem encountered in both groups was sexual desire.

COMMENTARY

Do you treat fibromyalgia in your practice? Do you even believe that it exists? The answer to the first question is a resounding "yes" whether you realize it or not, ie, you are likely seeing patients with fibromyalgia whether they are labeled as such or not. The answer to the second question is up to you. If you don't believe that it is a real clinical entity, then you need to have some explanation for the myriad of pains and symptoms that so many women have. Personally, I'm a big believer, but my bias is that of someone who has an office practice that focuses on pelvic pain disorders. Consider the following:

1. Fibromyalgia occurs in 2-4% of the general population, but it is estimated that up to 90% of patients are female. (That's our practice, by definition).
2. The most characteristic symptoms are generalized pain, stiffness, fatigue, and poor sleep. (Sound familiar?)
3. Fibromyalgia symptoms often follow an episode of infection, trauma, or mental stress. (I think a few of our patients may have some of those episodes, don't you?)
4. Up to 50% of patients with fibromyalgia have a current or past history of depression.

In the generic practice that focuses on women's health, sexual functioning is a major focus, either overtly or at least just beneath the surface. Just asking about it often brings forth an unexpected flood of emotions. In the routine visit, just asking whether the patient has any sexual concerns allows her to discuss it now or gives her permission to ask at a later time. It is well-known that sexual functioning can be compromised by pain syndromes but also poor body image and/or suboptimal health overall.

In this study, we are provided interesting insights into what appears in our practices very frequently. The interplay of chronic pain states and sexual functioning as well as clinical depression is an intricate web that can be overwhelming in a busy practice. The practitioner can be a great source for rational discussion and sort the issues out by recognizing that one often leads to the others. When we see patients who present with chronic pain, asking about depression or sexual functioning should be included. When a patient complains of sexual problems, inquire into depression and pain.

Remember, where there's smoke, there's fire. ■

CME Question

4. In patients with fibromyalgia, the most common sexual dysfunction is:

a. diminished desire.
b. anorgasmia.
c. dyspareunia.
d. sexual aversion.
e. lack of satisfaction.

Answer: (a)

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Treating Opioid-Dependent Patients with OAT

A Perspective article in the Jan. 17 *Annals of Internal Medicine* reviews pain management in patients with a history of opioid addiction who are receiving opioid agonist therapy (OAT) with maintenance methadone or buprenorphine. These patients present unique challenges that frequently result in suboptimal treatment of acute pain.

The authors provide an excellent review of these challenging patients and point our 4 common misconceptions: 1) Maintenance opioids provide analgesia—not only is this not the case, but OAT may reduce the effectiveness of standard pain relief measures; 2) Opioids for analgesia may result in addiction relapse—there is no evidence that treatment of acute pain triggers relapse; 3) The additive effects of opioid analgesics and OAT may cause respiratory and CNS depression—tolerance to the respiratory and CNS effects of opioids develops rapidly and is not exacerbated by acute therapy; 4) Reporting pain is drug-seeking behavior—as long as there is clinical evidence of pain, or an acute injury, pain may be safely treated. Drug seeking and manipulation is more likely characterized by vague reports of long-term pain than requests for short term pain relief. Plus, patients on OAT are less likely to experience euphoria associated with coadministered opioids, so there is less incentive to drug seek.

The authors provide specific pain treatment recommendations for patients on methadone and buprenorphine. They conclude, "Addiction elicits neurophysiologic, behavioral, and social responses that worsen the pain experience and complicate provision of adequate analgesia. These complexities are heightened for patients with opioid dependency who are receiving OAT, for whom the neural responses of tolerance or hyperalgesia may alter the pain experience. As a consequence, opioid analgesics are less effective; higher doses administered at shortened intervals are required. Opioid agonist therapy provides little, if any, analgesia for acute pain. Fears that opioid analgesia will cause addiction relapse or respiratory and CNS depression are unfounded. Furthermore, clinicians should not allow concerns about being manipulated to cloud good clinical assessment or judgment about the patient's need for pain medications. Reassurance regarding uninterrupted OAT and aggressive pain management will mitigate anxiety and facilitate successful treatment of pain in patients receiving OAT" (Alford DP, et al. *Ann Intern Med*. 2006;144:127-134).

Long-Term Effects of Warfarin Use

Warfarin use may be associated with osteoporosis and fractures in men, but not women, with atrial fibrillation, according to new study. In a retrospective cohort study of Medicare benefici-

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aries with atrial fibrillation in United States, 4461 patients on long-term warfarin therapy were compared to 7587 patients who were not prescribed warfarin. The adjusted odds ratio of fracture was 1.25 in patients who took warfarin (95% CI, 1.06-1.48). The odds ratio for men was 1.63, and a nonsignificant 1.05 for women. In patients who were prescribed warfarin for less than one year, the risk of osteoporotic fracture was not increased significantly. The authors speculate that since warfarin blocks vitamin K dependent clotting factors, it may also block vitamin K dependent osteocalcin and other bone matrix proteins. Interestingly, use of beta blockers reduced the risk of fracture in this population. The authors conclude that long-term use of warfarin was associated with osteoporotic fractures in men with atrial fibrillation, and that beta-blockers may be somewhat protective (Gage BF, et al. *Arch Intern Med*. 2006;166:241-246).

Statins' Multiple Benefits

Mounting evidence suggest that statins have benefits beyond their ability to lower LDL cholesterol. Multiple studies show that statins reduce inflammation in patients without heart failure. Now, 2 new studies suggest that they also reduce inflammation in patients with heart failure. In a study from Emory University, 108 patients with nonischemic heart failure were randomized to atorvastatin 20 mg per day or placebo. Inflammatory markers such as C reactive protein, interleukin-6, and TNF-alpha were all reduced in the atorvastatin group. Atorvastatin treated patients also showed an improvement in LVEF from 0.33-0.37 over one year (P = 0.01) (Sola S, et al. *J Am Coll Cardiol*. 2006;47:332-337).

A second study, from Harvard, in patients with heart failure showed that atorvastatin 10 mg/ day led to an 8% reduction in TNF receptor 1, a 37% reduction in C reactive protein, and a 17% reduction in endothelin-1 (Mozaffarian D, et al. *Am J Cardiol*. 2005;96:1699-1704). Atorvastatin may also have anti-thrombotic effects in patients with unstable angina according to a study from Greece. Forty-five patients with normal cholesterol levels and unstable angina were randomized to 10 mg of atorvastatin or placebo, starting right after hospital admission and continuing for 6 weeks. After one week of treatment circulating levels of anti-thrombin III, factor V, and von Willebrand factor were all significantly reduced in the atorvastatin group (Tousoulis D, et al. *Int J Cardiol*. 2006;106:333-337).

FDA Actions

The FDA has approved the first inhaled insulin for the treatment of adults with type I and type 2 diabetes. Inhaled insulin, a powder form of recombinant human insulin, has been in development for over 10 years, and has been the subject of intense scrutiny by the FDA. Concerns over long-term safety, particularly in people with underlying lung disease, has delayed approval, and safety in children and teenagers is still under investigation. Inhaled insulin is delivered through a device that is significantly larger than an asthma inhaler and, even folded, is the size of a flashlight. A blister pack of insulin powder is inserted into the device, which is then triggered. It is not to be used by smokers or people who quit smoking within last 6 months, and is not recommended for people with asthma, bronchitis, or emphysema. The FDA also recommends pulmonary function testing prior to starting inhalation therapy, and every 6 to 12 months thereafter. Although the product is approved for treatment of both type I and type 2 diabetes, fewer than 30% of type I diabetics achieve adequate control with inhaled insulin alone. Inhaled insulin is a joint effort by Pfizer, Sanofi-Aventis, and Nektar Therapeutics. It will be marketed under the trade name Exubera.

The FDA has approved an intravenous form of Ibandronate that can be administered every 3 months for the treatment of postmenopausal osteoporosis. The 3 mg dose is injected intravenously over 15 to 30 seconds by a healthcare professional. The drug is an option for women who cannot take pills or are unable to sit upright for 30 to 60 minutes after taking an oral bisphosphonate. Efficacy with the injectable form of ibandronate was better than once-a-day oral dosing of Ibandronate 2.5 mg in a study of over 1300 women with osteoporosis. Intravenous and oral forms of the drug were equally well tolerated. The FDA is recommending measurement of serum creatinines prior to administration each dose. Ibandronate is also approved is a 2.5 mg once a day oral dose and a 150 mg monthly oral dose. All 3 formulations are marketed as Boniva.

Berlex's combination estradiol-levonorgestrel patch (Climara Pro) has been approved for the indication for prevention of postmenopausal osteoporosis in women with an intact uterus. The patch was previously approved for the indication of moderate to severe vasomotor symptoms associated with menopause. The osteoporosis indication was based on a 2-year, double-blind, randomized trial that showed that the estradiol-levonorgestrel patch was associated with significant maintenance of bone density compared to placebo. ■