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## INSIDE



# Are You Screening for Depression in Your Practice?

ABSTRACT & COMMENTARY

WE ARE FREQUENTLY REMINDED THAT DEPRESSION IS MORE common in women (2:1 vs men), significantly increases morbidity and mortality, and even affects the development of the patients' children. Because the United States Preventive Services Task Force has recommended screening adults for depression, LaRocco-Cockburn and colleagues set out to determine what the current "state of the art" was (ie, identify the frequency of depression screening, determine the attitudes of practitioners toward screening, and pinpoint the factors that may affect the use of depression screening).

Obstetrician-gynecologists in the state of Washington were surveyed, with 282 individuals eligible for data analysis. Of interest, 49% were in a private group partnership, 68% had attended a CME course in the past 5 years where depression was discussed, and 41% considered themselves primary care physicians. Forty-four percent responded that they always or often screened for depression, 41% reported screening sometimes, and 15% said they never did. The methods used (often more than one method was used by a physician) included: questioning patients regarding mood/mental health (81%); short, validated tool (32%), validated patient self-report (16%); and validated interview (7%).

Other important findings included: 90% agreed that screening will improve the detection rate, but only 58% agreed that screening would lead to improved treatment outcomes; 65% agreed that OB/GYNs should screen for depression; only 24% felt that their patients did not want them to address psychosocial problems; 73% felt that time constraints would interfere with screening all patients; and only 32% felt that they had been appropriately trained to treat depression (LaRocco-Cockburn A, et al. Obstet Gynecol. 2003;101: 892-898).

### COMMENT BY FRANK W. LING, MD

All right, so I admit that this isn't the rigorous scientific article that you're used to seeing summarized in this publication. As your "down in the trenches," primary care advocate, I wanted to let you know what your colleagues are up to in order to see how you com-

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pare. When we consider that up to one-third of women will experience clinically significant depression during their lifetime, the importance of appropriate diagnosis and treatment becomes readily apparent.

Admittedly, this paper is flawed. (Aren't they all to some extent?) For example, these were physicians in a single state. Also, the study may be limited by responder bias (ie, the respondents may have been more interested in depression and, therefore, more likely to respond). There are useful lessons to be learned, however. Those respondents who had positive attitudes toward depression screening, psychosocial concern, and ease of screening were more likely to screen for depression in their practice. A younger-aged physician was more likely to have been trained to treat depression.

These physicians reported that time constraints, adequacy of training, and whether screening improves outcomes represented barriers to performing screening for depression in their practices. So where do you stand on this? What about the role of depression in the various clinical scenarios that we commonly face (eg, pelvic pain, infertility, spontaneous abortion, death and dying, premenstrual dysphoric disorder, postpartum depression, etc)? How do you screen for depression in your practice? Do you screen at all? Is there some quick and easy way to address the concerns that are raised by these results?

As far as mode of screening, just keep in mind the palindrome offered by Dr. Raphael Good many years ago: "How Are Things At Home (HATAH)." Some variation of this will provide a jumping off point for your patients and their symptoms of depression. As to the training issue, postgraduate courses or monographs are readily accessible wherever we turn. We have not yet proven that screening improves outcomes, but from my personal experience and certainly that of so many of our colleagues, the many cases in which depression has been successfully identified and treated provide enough motivation to continue the practice.

So I ask once again, where do you stand on screening for depression? ■

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# How Much Does Tight Glucose Control Diminish Fetal Macrosomia in Diabetes?

ABSTRACT & COMMENTARY

***Synopsis:*** *Fetal growth acceleration is identifiable by ultrasound at about 24 weeks. "Normal" parameters of glucose control during the first trimester and throughout pregnancy do not seem to be related to the growth potential of the LGA fetus of a diabetic mother. Fluctuations in glucose levels rather than basal levels are probably more determinant in fetal growth acceleration.*

**Source:** Greco P, et al. *Fetal Diagn Ther*. 2003;18(6): 437-441.

THE LITERATURE HAS BEEN CONFUSING REGARDING the relationship between glucose control in diabetes and fetal size. Fetal macrosomia is a complication worth averting, and it has been convenient to think that tight control of blood sugars would always do this.

Greco and colleagues from Italy set out to assess fetal growth in Type I diabetics who were in a highly regimented program of glucose monitoring from the first trimester of pregnancy (capillary glucose levels 7 times a day and glycosylated hemoglobin values once a month). The 98 women in the study all had ultrasound examinations in the first trimester, at 16-18 weeks and then every 3 weeks thereafter. The results were intrigu-

ing and, perhaps, discouraging on the surface. Greco et al found that mean glucose levels did not correlate statistically with fetal size, as reflected by the fetal abdominal circumference (AC) and birth weight. The same lack of relationship was found with glycosylated hemoglobin.

They did find that the AC of fetuses destined to be large for gestational age (LGA) infants were larger at 24 weeks than the appropriate for gestational age (AGA) babies in the study. This trend continued throughout pregnancy, as the LGA fetuses maintained growth profiles that were consistently different from AGA fetuses.

**COMMENT BY JOHN C. HOBBINS, MD**

There is no doubt that fetal macrosomia is associated with out-of-control diabetes. There are some studies that show that bringing blood sugar levels into reasonable range might reduce the incidence of macrosomia, while other studies suggest that tight glucose control might not be the answer. The Italian study shows that mean blood sugars (representing short-term control) and glycosylated hemoglobin (representing long-term control) did not correlate with fetal size at birth. While this study was undertaken in a group of patients who were all very tightly monitored, it in no way implies that attempting to control blood sugars will be to no avail in all pregestational diabetics.

In fact, the full story on fetal macrosomia is not out yet. For example, the incidence of LGA (above the 90 percentile) in this study was almost doubled (17.3%) over the expected rate despite scrupulous glucose monitoring.

The seemingly simplistic idea that maternal/fetal hyperglycemia triggers release of fetal insulin—a stimulator of fetal growth—certainly should not be discarded, since the fetal pancreas may respond more to large swings in glucose levels that would not be reflected in the mean glucose levels analyzed in the Italian study. The fact that other agents (now being explored) might be working in tandem with fetal insulin could explain why the LGA fetuses in this study fell off the curve by the 24th week of gestation.

There is also good news here. I like the idea of assessing fetal growth with AC alone since infants of diabetics have large livers and an overabundance of triglycerides in the subcutaneous tissue, both of which would be reflected in a cross-sectional view of the upper fetal abdomen. The size of the head and limbs, included in all standard biometric assessments and incorporated into estimations of fetal weight, more often take into account genetic predispositions, rather than fetal corpulence. The above study suggests that if the AC is within normal limits by (let us say) 26 weeks, it is very unlikely that the fetus would be macrosomic at birth. In contrast, if the AC is ahead of dates at this point, then the likelihood of macrosomia at birth is substantial and would warrant a careful evaluation of fetal size and evidence of body-to-head disproportion before birth. This, in turn, could play a role in labor management.

In summary, the above study in no way suggests that diabetics need not have comprehensive glucose monitoring since failure to do so could undoubtedly result in a higher rate of macrosomia. However, the study shows that even tight control (by their regimen) will not completely prevent macrosomia, suggesting that there is more to macrosomia than hyperglycemia alone. Last, the macrosomic die seems to be cast by mid-pregnancy.

**Suggested Reading**


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# CT Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults

ABSTRACT & COMMENTARY


***Synopsis:*** *When analyzed using 3-dimensional methods, virtual colonoscopy achieves comparable accuracy in screening asymptomatic adults for colonic polyps as optical colonoscopy.*



**Source:** Pickhardt PJ, et al. *N Engl J Med*. 2003; 349:2191-2200.


Pickhardt and colleagues compared the performance of computed tomographic (CT), "virtual" colonoscopy with standard optical colonoscopy for the detection of colorectal neoplasia in an asymptomatic population. A total of 1233 adults aged 50-79 years underwent same-day virtual colonoscopy followed immediately by optical colonoscopy. The sensitivity of virtual colonoscopy for adenomatous polyps was 93.9% for polyps ≥ 8 mm in diameter and 88.7% for those ≥ 6 mm. The sensitivity of optical colonoscopy was 92.2%

and 79.6%, respectively. Also, CT identified clinically important, extra-colonic findings in 56 patients, 5 of which turned out to be cancerous. Two abdominal aortic aneurysms were found and repaired. The mean time spent by patients was 14 minutes for CT and 31 minutes for optical colonoscopy. Most patients preferred the CT colonoscopy, even though they rated it as equally uncomfortable (because the patient must introduce sufficient air to achieve pneumocolon for the CT to be readable). The only apparent drawback to virtual colonoscopy is that in practice, polyps or other significant lesions identified on screening virtual colonoscopy would require optical colonoscopy for biopsy afterward. In contrast, with optical colonoscopy, the biopsy can be done at the time of the procedure. The other limitations to the use of virtual colonoscopy are the need for dedicated training of radiologists and technologists and the lack of availability of the software systems that permit 3-dimensional analysis.

**COMMENT BY SARAH L. BERGA, MD**

This article grabbed my attention because I had just seen a glaring example of direct-to-consumer advertising in the form of a huge billboard along the interstate advocating virtual colonoscopy. I had not read too much about this technique in the medical literature, as most of the published debate has focused on the pros and cons of occult heme testing from stool samples vs standard sigmoidoscopy vs optical colonoscopy. Although I was not necessarily the intended consumer, the billboard worked well in that it garnered my professional attention. Interestingly, most professional organizations that make screening recommendations do not even endorse optical colonoscopy because of the cost and risk. Rather, they generally advocate sigmoidoscopy or occult heme testing. However, optical colonoscopy does have a higher sensitivity, if only because more of the colon is examined and colonic cancers are evenly distributed throughout the length of the colon. (I like to think of a sigmoidoscopy as similar to doing a screening mammogram of only 1 breast.) Since colorectal cancer is the second leading cause of cancer-related death, it is prudent to recommend some form of screening. In average-risk patients, the guidance has been to start screening at age 50 years.

Most colorectal cancers are believed to arise within benign adenomatous polyps, the removal of which markedly decreases the incidence of colorectal cancer. In the discussion of the present article, Pickhardt et al note that the number of patients who would require subsequent optical colonoscopy for removal of polyps identified on virtual colonoscopy depends on the recommendation regarding the size of the polyp that must be removed. If the cut-off is 6 mm, then 30% of patients in the present study would have required follow-up optical colonoscopy. Pickhardt et al recommend removal for polyps ≥ 8 mm, in which case only about 15% of the study population would have required optical colonoscopy. Of note, only about half of the eligible population has not undergone screening of any type. Thus, a technique that works and has high patient acceptance with low medical risk would represent a true medical advance.

The erstwhile OB/GYN who has time to do appropriate well-care counseling clearly should include a discussion of screening for colon cancer. However, to do this, one has to have both an opinion about and the time to make a recommendation. The present article is intended to help with forming an opinion. I have still not conquered the time barrier. Assuming comparable cost (a topic not covered in the article), it would appear that virtual colonoscopy has higher patient acceptance and comparable sensitivity and clearly can be recommended to interested patients older than 50. If the first optical colonoscopy is negative in an average-risk, asymptomatic individual, current recommendations suggest that the next one be done in 10 years. Given the comparable sensitivity, one assumes that a similar recommendation would hold for a negative virtual colonoscopy.

# Discontinuing Dopamine Agonist Treatment for Hyperprolactinemia

ABSTRACT & COMMENTARY

***Synopsis:*** *Cabergoline can be safely withdrawn in patients with normalized prolactin levels and no evidence of tumor. However, because the length of follow-up in this study was insufficient to rule out a delayed increase in the size of the tumor, it suggests that patients be closely monitored, particularly those with macroprolactinomas, in whom renewed growth of the tumor may compromise vision.*

**Source:** Colao A, et al. *N Engl J Med*. 2003;349: 2023-2033.

COLAO AND COLLEAGUES FROM THE FEDERICO II University of Naples, Italy, terminated cabergoline therapy after 3-4 years in 200 patients (25 with hyperprolactinemia and no evidence of a pituitary tumor, 105 with microprolactinomas, and 70 with macroprolactino-

mas). The guidelines for discontinuing treatment included a normal prolactin level and either no evidence of a tumor or 50% or more tumor reduction on MRI. The patients were followed for 2-5 years with the following results:

**Nontumoral hyperprolactinemia:** 24% of the female patients had a return of hyperprolactinemia, but menses remained normal.

**Microadenomas:** 30% had a return of hyperprolactinemia without MRI evidence of tumor recurrence; 20% of the female patients developed oligomenorrhea; none had galactorrhea.

**Macroadenomas:** 36% had a recurrence of hyperprolactinemia, but none had evidence of tumor growth.

In those patients with a recurrence of elevated prolactin levels, the average time required for recurrence was 12-18 months. The major clinical conclusions of this study are: 1) Dopamine agonist can be discontinued, and most patients have no recurrence of hyperprolactinemia; 2) Even if hyperprolactinemia recurs, tumor growth is very unlikely; and 3) Pituitary tumor treatment with a dopamine agonist should be maintained for at least 1-2 years.

## COMMENT BY LEON SPEROFF, MD

The low rate of side effects and the once-weekly dosage make cabergoline the drug of choice for the treatment of hyperprolactinemia. There is even evidence to indicate that response, especially tumor reduction, is superior to that with bromocriptine, and tumors resistant to bromocriptine will respond to cabergoline.

Treatment of prolactin-secreting pituitary adenomas with dopamine agonists is preferred because of the relatively high rate of recurrence after pituitary surgery. However, it has long been recognized that discontinuation of medical therapy is followed by recurrence of hyperprolactinemia. But renewed growth of a prolactin-secreting tumor is uncommon, most likely because these tumors rarely grow anyway. Nevertheless, some tumors can resume growth, and on-going surveillance will be necessary.

This study highlights some major points of disagreement regarding patient management comparing gynecologic endocrinologists with medical endocrinologists. Medical endocrinologists generally believe that elevated prolactin levels and microadenomas need to be treated with dopamine agonists. Gynecologic endocrinologists generally believe that microadenomas need be treated only if the patients are seeking fertility or experiencing disturbing galactorrhea. The fundamental reason for our belief is the rarity of tumor growth in these patients. Thus, I prefer to treat the amenorrhea or menstrual irregularity associated with elevated prolactin levels with oral contraceptives. In other words, there is no harm in allowing prolactin levels to remain elevated, and it is not necessary to use a dopamine agonist to restore normal menstrual function. I recommend the following management:

### Microadenomas

The treatment of microadenomas should be directed to alleviating 1 of 2 problems: infertility or breast discomfort. Treatment with a dopamine agonist is the method of choice. The major therapeutic dilemma can be expressed by the following question: Should chronic dopamine agonist treatment be used to retrieve ovarian function in those patients with hypoestrogenic amenorrhea, or should estrogen treatment be offered? I do not advocate widespread dopamine agonist therapy for those patients not interested in becoming pregnant. This conservative approach is supported by documentation of a benign clinical course with spontaneous resolution in many patients.[1-3] Patients with hypoestrogenic amenorrhea are encouraged to be on an estrogen therapy program to maintain the health of their bones and the vascular system. Low-dose oral contraception is recommended for those patients who require contraception. Estrogen-induced tumor expansion or growth has not been a problem in both my experience and in that of others.[4,5]

### Macroadenomas

Dopamine agonist treatment is the treatment of choice for macroadenomas, using as low a dose as possible. Once shrinkage has occurred, the daily dose should be progressively reduced until the lowest maintenance dose is achieved. The serum prolactin level can be used as a marker, checking levels every 3 months until stable. In many (but not all) patients, control of tumor growth correlates with maintenance of a baseline prolactin level. Withdrawal of the drug can be associated with regrowth or reexpansion of the tumor, and, therefore, treatment must be at least several years. If there is a good response in prolactin levels, and if present, visual field defects, the MRI should be repeated after 1 year of treatment to establish size reduction of the tumor. Some patients will prefer surgery rather than long-term medical treatment, and it is certainly a legitimate option. In view of better results claimed in more recent times, this choice should be presented to the patient. Transsphenoidal surgery is recommended when suprasellar extension or visual impairment persists after dopamine agonist treatment of a macroadenoma. For some patients, side effects with dopamine

agonist treatment and difficulty with medication compliance make surgery a reasonable alternative. Because tumor recurrence after surgery is high, radiotherapy should be considered. All patients receiving radiotherapy require ongoing surveillance for the development of hypopituitarism. Surgery should be considered as a debulking procedure for very large tumors with or without invasion prior to long-term dopamine agonist therapy. Even though prolactin levels usually increase when dopamine agonist treatment is discontinued after several years, many tumors (70-80%) do not regrow.[6,7] Pregnancy should be deferred until repeat imaging confirms shrinkage of the macroadenoma.

Approximately 10% of macroadenomas do not shrink with dopamine agonist therapy. The failure of a tumor to shrink significantly in size despite a normalization of prolactin levels can be consistent with a nonfunctioning tumor that is interrupting the supply of dopamine to the pituitary by stalk compression. Early surgery is indicated. A tumor that continues to grow despite dopamine agonist treatment may be a rare carcinoma.

### Long-Term Follow-Up

Because these tumors can grow slowly, it is appropriate in the absence of symptoms to evaluate patients with microadenomas annually for 2 years. The evaluation consists of a measurement of the prolactin level and imaging of the sella turcica. If the course is unchanged, annual evaluation can be limited to measurement of the prolactin level. It should be noted that progressively increasing prolactin levels have been observed without associated tumor growth of a microadenoma. The rare microadenoma that grows deserves treatment. Patients with macroadenomas deserve an initial period of follow-up after treatment every 6 months, and if the adenoma appears to be clinically stable, prolactin levels should be measured annually. MRI is reserved for situations suggestive of tumor expansion. If the clinician and patient need reassurance regarding tumor size, imaging intervals can be prolonged if the tumor is stable (eg, at 1 year, 2 years, 4 years, 8 years). Tumor expansion and recurrent tumors after surgery or radiotherapy deserve a trial of treatment with a dopamine agonist.

Patients who have been on dopamine agonist treatment for 2-5 years with successful tumor size reduction can have a gradual reduction, and eventually stopping of treatment, followed by monitoring of prolactin levels every 3 months. If a normal prolactin level is maintained, I recommend an imaging study 1 year later. Of course, tumor reexpansion requires resumption of treatment with the gradual program that should always be used when starting therapy. ■


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# Differences in Treatment and Outcome Between African-American and White Women with Endometrial Cancer

ABSTRACT & COMMENTARY


***Synopsis:*** *African-American women with endometrial cancer are significantly less likely to undergo primary surgery and have significantly shorter survival than white women with endometrial cancer.*



**Source:** Randall RC, Armstrong KJ. *Clin Oncol*. 2003;21:4200-4206.


Randall and Armstrong recently reported an interesting study in which they analyzed 1992-1998 Surveillance, Epidemiology, and End Results (SEER) data for 21,561 women with epithelial cancers of the endometrium with the objective of investigating disparities in treatment and outcomes between African-American and white women with endometrial cancer. Sequential Cox proportional hazard models were used to determine the association between tumor characteristics (stage, grade, and histologic type), sociodemographic characteristics (age and marital status), and treatment (surgery and radiation therapy) and racial difference in mortality. The unadjusted hazard ratio (HR) for death from endometrial cancer for African-American women compared with white women was 2.57.

However, African-American women were significantly more likely to present with advanced-stage disease and have poorly differentiated tumors or tumors with an unfavorable histologic type and were significantly less likely to undergo definitive surgery at all stages of disease. Adjusting for tumor and sociodemographic characteristics lowered the HR for African-American women to 1.80. Further adjust-

ment for the use of surgery reduced the HR to 1.51. The association between surgery and survival was stronger among white women (HR, 0.26) than among African-American women (HR, 0.44). Randall and Armstrong concluded that African-American women with endometrial cancer are significantly less likely to undergo primary surgery and have significantly shorter survival than white women with endometrial cancer. They further noted that racial differences in treatment are associated with racial differences in survival and that the association between use of surgery and survival is weaker among African-American than white women, raising the question about potential racial differences in the effectiveness of surgery.

**COMMENT BY DAVID M. GERSHENSON, MD**

Approximately 40,000 American women are diagnosed with endometrial cancer in the United States annually. Based on SEER data, the survival rate for African-American women with endometrial cancer was approximately 59%, compared with 86% for white women. As noted in this study, prior studies revealed that African-American women have a higher incidence of poorly differentiated tumors or tumors with unfavorable histologies. In addition, most studies indicated that, even after controlling for comorbid conditions and socioeconomic status, these differences persist. The present study focused on the relationship between treatment and survival. Randall and Armstrong found that, at all stages, African-American women were less likely to receive definitive surgery. They also point out, however, this relationship may not be causal. By the very act of performing surgery, which may reclassify apparent early stage patients with more advanced disease into a higher stage category, survival is improved.

The reasons for a lower rate of surgery in African-Americans remain somewhat elusive. Partial explanations include differences in extent of disease, access to care, or comorbid conditions. One of the problems with any study using the SEER database is that information is limited. For instance, the SEER database does not include much of the sociodemographic data or comorbidity data that would potentially provide insights into some unresolved issues. As with several other diseases and conditions, further studies will be necessary to elucidate the reasons for differences in outcome between racial/ethnic groups. Fortunately, health disparities research is of growing interest and is increasingly being funded. ■

*Special Feature*

# Unilocular Ovarian Cysts in Postmenopausal Women: Surgery vs Expectant Management

*By David M. Gershenson, MD*

When I was a resident in obstetrics and gynecology in the mid-1970s, and well beyond, the dogma was that any ovarian cyst or mass in a postmenopausal woman was abnormal and required surgical resection. Postmenopausal women weren't supposed to have ovarian cysts, and the possibility of cancer was looming largely, Of course, at that time, ultrasound was only beginning to be used in clinical practice, and then, almost exclusively in the practice of obstetrics.

Even with the advent of gynecologic sonography, however, it took almost 25 years to accumulate enough experience with postmenopausal cystic ovarian masses to begin to formulate management and treatment guidelines. This odyssey was also facilitated by the increasingly liberal use of computerized tomography and the discovery of the tumor marker, serum CA 125, in the early 1980s. In 2003, we have incontrovertible evidence that the vast majority of postmenopausal women with unilocular ovarian cysts up to 10 cm in diameter do not require surgery. How did we arrive at that judgment?

With increasing use of pelvic sonography for evaluation of women with gynecologic complaints or adnexal masses, reports began to emerge in the early 1980s describing ovarian cysts in postmenopausal women. These reports documented the apparent low rate of malignancy associated with unilocular ovarian cysts.[1-8] Of postmenopausal women with unilocular ovarian cysts < 5 cm, only 3 of 209 (1%) were found to have a malignancy. Of unilocular ovarian masses in the 5-10 cm range, 1 of 21 (5%) postmenopausal women had a malignancy, which turned out to be only a tumor of low malignant potential.

In 1998, Bailey et al reported their experience with the University of Kentucky Ovarian Cancer Project.[9] The Kentucky group had screened 7705 asymptomatic postmenopausal women with transvaginal ultrasound and identified 256 women (3.3%) with unilocular cystic ovarian masses. This included 231 women with ovarian cysts < 5 cm and 25 women with ovarian cysts in the 5-10 cm range. Spontaneous resolution of these unilocular ovarian cysts occurred in 54.3% of women 50-60 years of age and

in 23.9% of women older than 60 years of age. All of the 45 women with persistent unilocular ovarian cysts subsequently underwent either laparoscopy or laparotomy with resection of the ovarian masses. None had a cancer. The histology of the ovarian masses in these women included a serous cystadenoma in 32, paratubal cyst in 4, paraovarian cyst in 3, endometriotic cyst in 2, mucinous cystadenoma in 2, hydrosalpinx in 1, and peritoneal cyst in 1.

More recently, in the September issue of *Obstetrics and Gynecology*, 2 reports further strengthen the data regarding unilocular ovarian cysts in postmenopausal women. In an update of the Kentucky group, Modesitt et al[10] reported on 15,106 asymptomatic women at least 50 years old who underwent transvaginal sonography from 1987 to 2002. With almost twice the numbers in the 1998 report, multiple screens per individual over time, and probable improved technology, they found a higher rate of unilocular ovarian cysts (in 3259 women, or 18%) and a higher rate of spontaneous cyst resolution (in 2261 women, or 69.4%). Furthermore, they noted that a septum developed in 537 (16.5%), a solid area developed in 189 (5.8%), and 220 (6.8%) persisted as a unilocular lesion. No woman in this study with an isolated unilocular cyst has developed ovarian cancer. However, 27 women were diagnosed with ovarian cancer, and 10 had been previously diagnosed with simple ovarian cysts. It is important to note that all 10 of these women developed another morphologic abnormality, experienced resolution of the cyst prior to developing cancer, or developed cancer in the contralateral ovary.

Nardo and colleagues,[11] in a report from the Unietd Kingdom, conducted an observational study of 226 postmenopausal women with unilocular ovarian cysts < 5 cm who were followed up for a 5-year period. They noted no change in ovarian cyst diameter and serum CA 125 levels in 172 (76.1%) of the women. Fifty-four women had an increase in cyst diameter, of which 6 (11.1%) also had an increase in serum CA 125 levels. All 54 women with suspicious ovarian pathology and 84 without suspicious pathology underwent surgery. Two of the 54 women were diagnosed with stage IB, grade 1 serous carcinoma; both women had elevated serum CA 125 levels.

In summary, in postmenopausal women with unilocular ovarian cysts that do not change in their ultrasonic appearance and in whom serum CA 125 levels remain normal, expectant management appears to be most appropriate. The malignancy rate in this group of patients is exceedingly low, but never zero. It may be slightly higher in women whose cyst is 5-10 cm in diameter compared with those whose cyst is < 5 cm. According to the Kentucky study, a very high proportion of these cysts will resolve spontaneously.[10] Indications for surgical intervention may include symptomatology, a rise in serum CA 125 levels, or a change in the sonographic characteristics to include a septum or solid area.

If an asymptomatic unilocular ovarian cyst is found in a postmenopausal woman with a normal serum CA 125, how often should she be screened? There is no clear answer. In the British study, patients had a repeat screen in 6 months and then annually thereafter. If one discovers a new unilocular ovarian cyst in a postmenopausal woman (in combination with a normal serum CA 125), my bias would be to repeat the ultrasound and serum CA 125 in 6-12 weeks, and then every 3-6 months × 2, and then every 6-12 months thereafter. This may be overkill, but only future studies will elucidate the optimal interval. ■

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## *CME Question*

1. **The following statements regarding prolactin-secreting pituitary tumors are true *except*:**
   a. Prolactin levels always return to baseline elevations after treatment with dopamine agonists.
   b. Microadenomas do not always need to be treated with dopamine agonists.
   c. Macroadenomas should be treated with dopamine agonists.
   d. Macroadenomas do not have to be treated indefinitely.

**Answer:** 1 (a)

# PHARMACOLOGY WATCH

## Vioxx Might Control Postoperative Knee Pain

Oral rofecoxib (Vioxx) may have a role in controlling postoperative pain patients undergoing knee surgery. Researchers in Chicago enrolled 70 patients who were undergoing total knee arthroplasty and randomized them to rofecoxib 50 mg the day prior to surgery, 1-2 hours prior to surgery, and for 5 days postoperatively, then 25 mg daily for another 8 days; or matching placebo at the same times. The main outcome was postsurgical analgesic consumption and pain scores, as well as nausea and vomiting, joint range of motion, sleep disturbance, and patient satisfaction with analgesia and hematologic anticoagulation parameters. Rofecoxib resulted in significantly reduced use of epidural analgesia and in-hospital opioid consumption ($P < .05$). Pain scores were also lower in the rofecoxib group while in the hospital ($P < .001$) as well as 1 week after discharge ($P = .03$). Rofecoxib also resulted in less postoperative nausea, a decrease in sleep disturbance, as well as increased knee flexion at 1 month—including a shorter time in physical therapy to achieve effective joint range of motion. The drug had no effect on warfarin usage or INR levels postoperatively. Interestingly, Buvanendran and colleagues did not include changes in renal function or evidence of GI intolerance in the study analysis. They did conclude however that rofecoxib is effective at reducing postoperative pain and opioid consumption after major orthopedic surgery (*JAMA*. 2003;290:2411-2418).

### *Echinacea Has No Value for URIs*

Just in time for winter, another study showed that *Echinacea* has no value for reducing the duration or severity of upper respiratory tract infections (URIs). The herbal remedy is commonly used worldwide for this indication. In this study of children in the Pacific Northwest, 707 URIs occurred in 407 children over 2 years. Three hundred thirty-seven URIs were randomized to treatment with *Echinacea* while 370 were assigned to placebo. *Echinacea* was begun at the onset of symptoms and continued throughout the infection for maximum of 10 days. Data analysis showed there was no difference in the duration of URIs with *Echinacea* or placebo ($P = .89$), and there was no difference in the overall estimate of severity of URI symptoms ($P = .69$). There was also no statistically significant difference between the 2 groups for peak severity of symptoms, number of days of peak symptoms, number of days of fever, or parental global assessment of severity of URI. Rash occurred during 7.1% of URIs treated with *Echinacea* and 2.7% of those tree with placebo ($P = .008$). The study concludes that *Echinacea* was not effective in treating URI symptoms in patients 2 to 11 years old but was associated with an increase in skin rash (*JAMA*. 2003;290:2824-2830).

### *Valsartan, Captopril Have Similar Benefits*

Valsartan and captopril have similar benefits in patients with myocardial infarction complicated

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by left ventricular systolic dysfunction, heart failure, or both, according to a new study. Previous studies have shown that ACE inhibitors reduce mortality and cardiovascular morbidity in this group, but it was unclear if angiotensin receptor blockers (ARBs) conveyed the same benefit. In this international study, nearly 15,000 patients with myocardial infarction were randomized to valsartan, captopril, or a combination of valsartan and captopril. The primary end point was death from any cause. The median follow-up was just more than 2 years. During that time, the death rate in all 3 groups was remarkably similar (979 of 4909 deaths valsartan, 958 of 4909 deaths captopril, 941 of 4885 deaths combination [hazard ratio valsartan vs captopril 1.0; 97.5% CI, 0.9-1.11; $P = 0.98$], [hazard ratio valsartan and captopril vs captopril, 0.98; 97.5% CI, 0.89-1.09; $P = 0.73$]). The valsartan plus captopril group had the most drug-related adverse events, while in the monotherapy groups valsartan was associated with more hypotension and renal dysfunction, while cough, rash, and taste disturbance were more common with captopril. Pfeffer and associates conclude that valsartan is as effective as captopril in patients with myocardial infarction who are at high risk for cardiovascular events, but combining valsartan with captopril did not offer an advantage (*N Engl J Med*. 2003;349:1893-1906).

## In-patients Likely to Continue Lipid Use

In-patients who are started on lipid-lowering therapy following coronary intervention are 3 times more likely to continue on the drugs compared to patients who are started on the same therapy as outpatients. Using data from the EPILOG trial in which patients underwent percutaneous coronary intervention for stable or recently unstable coronary artery disease, 175 patients were discharged from the hospital on lipid-lowering therapy and 1951 were discharged on no lipid-lowering therapy, with the intent to start them on treatment as outpatients. After 6 months of follow-up, 77% of patients who were started in the hospital were still taking lipid-lowering therapy compared with only 25% of those who were discharged without lipid-lowering therapy ($P < .001$). Aronow and colleagues suggest that initiation of lipid-lowering therapy in the hospital is effective strategy to enhance subsequent use of the drugs in these high-risk patients (*Arch Intern Med*. 2003;163:2576-2582).

## More on Metformin/Lactic Acidosis

When it comes to the relationship between metformin and lactic acidosis, the emperor may have no cloths. The drug, which has been used to treat type 2 diabetes for more than 40 years, has always carried with it the stigma that it may cause lactic acidosis in at-risk patients. Metformin hydrochloride is a biguanide that is similar in structure to phenformin hydrochloride, which was withdrawn from the market because of a documented risk of lactic acidosis. Metformin increases glucose oxidation without substantially affecting fasting lactate production and peripheral tissues unlike phenformin, and the true rate of metformin-associated lactic acidosis has never been demonstrated. Recently, researchers from Stanford performed a thorough review of the literature on this topic and performed a meta-analysis on 194 studies involving nearly 37,000 patient years in the metformin group and 30,000 patient years in the nonmetformin group. No cases of fatal or nonfatal lactic acidosis were found in either group. Their conclusion is that there is no evidence that metformin therapy is associated with an increased risk of lactic acidosis or with increased lactate levels compared with other antihyperglycemic treatments (*Arch Intern Med*. 2003;163:2594-2602). The study is important because metformin is an effective treatment for type 2 diabetes, and has some unique properties including stabilizing weight gain or even facilitating weight loss. The drug has also recently become multisource (generic) and is affordable for diabetic patients who must pay for their medications.

## FDA Notes

The FDA has approved tadalafil (Cialis), Eli Lilly and Icos Corp's entry into the lucrative phosphodiesterase inhibitor market. With the success of sildenafil (Viagra), and newcomer vardenafil (Levitra) already generating huge profits, Cialis is being touted as a longer acting, less expensive alternative for the treatment of erectile dysfunction. The drug, which exerts its effect over 36 hours, has already been dubbed "the weekend drug" in Europe, where it as been available for some time.

Bristol-Myers has received approval to market the first chewable oral contraceptive for women. The product is a new formulation of Ovcon 35 (norethindrone and ethinyl estradiol), which is spearmint flavored and can be chewed or swallowed whole. If chewed than swallowed, the woman should drink a full 8 oz of liquid immediately afterward to make sure the entire dose reaches the stomach. ■

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## St John's Wort and Drug Interactions

**Source:** Markowitz JS, et al. *JAMA*. 2003;290:1500-1504.

THE CYTOCHROME P450 SYSTEM IS responsible for the metabolism of the majority of currently prescribed medications. The 2 most common P450 pathways involved in drug metabolism are CYP 3A4 and 2D6, which together are responsible for metabolizing almost three quarters of currently available medications. Any agent that either blocks or enhances either of these enzyme pathways can potentially induce medication toxicity (through drug accumulation) or reduce drug efficacy (through more rapid metabolic disposal).

St. John's Wort (SJW) is a popular over-the-counter agent used for depres- sion, the active ingredient of which is felt to be hypericum. Case reports have suggested that SJW might affect drugs as diverse as cyclosporine, indinavir, tricyclic antidepressants, simvastatin, and even oral contraceptives. For instance, it has been suggested that the enhanced activation of the CYP3A4 system by SJW might lead to increased metabolism of ethinyl estradiol in oral contraceptives, leading to unplanned pregnancy.

Markowitz and associates studied pharmacokinetics of substances metabolized by the 3A4 and 2D6 CYP systems when coadministered with SJW. A 2-fold increase in 3A4 activity was seen, but no effect upon 2D6 was found. Since many drugs are metabolized by the CYP 3A4 system, clini- cians must recognize which patients are taking SJW to minimize adverse effects upon medication pharmacokinetics. ■

## Serum Potassium and Stroke Risk Among Hypertensive Adults

**Source:** Smith NL, et al. *Am J Hypertens*. 2003;16:806-813.

OBSERVATIONAL DATA INDICATE THAT persons who consume greater levels of dietary potassium have both lowered blood pressure and reduced risk of stroke. This protective effect of dietary potassium intake is seen in both hypertensive and normotensive persons, though it is more pronounced in men than women. In some hypertension trials, serum potassium levels have shown an inverse relationship with stroke, but of course many of these subjects received diuretic therapy with an anticipatable decline in serum potassium, and these findings have not been consistent among all populations.

Using data from the Group Health Cooperative observational study (a Washington state-based HMO), Smith and colleagues evaluated the relationship between hypokalemia and subsequent ischemic (n = 593) or hemorrhagic stroke (n = 125) in this population of hypertensive adults compared to controls (n = 2397). Potassium status was defined by traditional levels of hypokalemia (potassium < 3.5) measured in the year prior to stroke.

Hypokalemia was associated with substantial increases in risk of stroke, both for ischemic (odds ratio, 2.04) and hemorrhagic (odds ratio, 3.29) stroke. Since no gradient of stroke risk through the normal range of potassium was discerned, the likelihood that it is indeed the hypokalemia that is etiologically related to stroke risk is further strength- ened. Use or non-use of diuretics did not affect the relationship between hypokalemia and stroke. The mechanism by which hypokalemia might aggravate stroke risk is uncertain. ■

## Skin Cancer Prevention and Detection Practices Among Siblings of Patients with Melanoma

**Source:** Geller AC, et al. *J Am Acad Dermatol*. 2003;49:631-638.

MORE THAN ONE-HALF MILLION Americans have invasive malignant melanoma (MEL), and the incidence of this disorder has risen an alarming 15-fold since World War II. Family members (first degree) of persons with MEL have as much as a 2-8- fold increased risk of developing MEL.

Recommendations by such agencies as the United States Preventive Services Task Force and the National Institute of Health include the suggestion that family members of patients with MEL should be provided skin cancer screening, risk education, and reduction of ultraviolet radiation exposure. When surveillance for MEL is carried out amongs family members, the stage at which MEL is discovered is earlier than that of the index case. Whether such recommendations are adequately used has not been studied.

Geller and associates contacted 585 siblings of 278 persons diagnosed with MEL within the previous 2 months. Although most of the siblings (62%) had examined their skin in the past year, only slightly more than half used sunscreen with at least SPF 15, and only

27% had received a skin cancer examination by a dermatologist. The message to family members of MEL victims about positive steps to maintain their own cutaneous health requires greater advocacy. ■

## TZDs and HF in People with Type 2 Diabetes

**Source:** Delea TE, et al. *Diabetes Care*. 2003;26:2983-2989.

THIAZOLIDINEDIONES (TZDS) OFFER numerous potential benefits in diabetic patients, including improved insulin-stimulated glucose disposal, decreased insulin resistance, and favorable lipid effects. One of the well-recognized adverse effects of TZDs is an increase in plasma volume, reflected by a decrease in hematocrit, weight gain, and edema. Although case reports of an association between TZDs and heart failure have been reported, no published study has specifically examined this issue.

Relying on a large health insurance claims database, Delea and colleagues compared data from type 2 diabetic patients receiving TZDs (n = 5441) with control subjects (n = 28,103) based upon observational data accrued August 1997-March 2001.

During the follow-up period, subjects receiving TZDs were more than 1½ times more likely to experience heart failure than control subjects (2.3% incidence vs 1.4%). This translates into an approximately 60% greater relative risk of heart failure for diabetics treated with TZDs than controls. On the other hand, having received a prescription for metformin in the 3 months before initiation of the observation period was associated with a lesser risk of heart failure, hence "antidiabetic treatment" per se cannot be held culpable.

Previous warnings have cautioned specifically about the combination of insulin with TZDs, indicating an increased risk of heart failure; in this study, however, no discernible difference in risk of heart failure between TZDs with, or without, insulin was seen. ■

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## Exercise Plus Behavioral Management in Patients with AD

**Source:** Teri L, et al. *JAMA*. 2003; 290:2015-2022.

ALTHOUGH ALZHEIMER'S DISEASE (AD) prompts clinicians to immediately address cognitive function, there is much less awareness of AD effect upon physical conditioning. AD patients have been found to be at greater risk of falls, fractures, rapid decline in mobility, and undernutrition. Pilot studies of exercise programs for AD patients have been promising, with benefits extending beyond simple conditioning to include favorable effects upon depression.

Home-based caregivers, for whom little guidance has been available about optimum techniques for exercise and behavioral management, provide much of the care for AD. This study randomized AD patients (n = 153) to traditional community care or an active exercise and behavioral management program. The active treatment group (patient and caregiver) received 12 sessions lasting 1 hour with instruction about exercise, strength training, balance, and flexibility, with a goal of at least 30 minutes of moderate intensity exercise daily. Supervised instruction occurred for 3 months, after which the patient and caregiver were "on their own"' for an additional 24 months.

When compared to persons who received "routine" care, at 3 months time there was a significant difference in the SF-36 (quality of life evaluation) and depression scores in favor of active treatment. Indeed, while improvements in scores were seen amongst the active treatment group, declines in scores were seen for traditional care. At 24 months, there were still significant differences between the 2 groups. Teri et al conclude that the robust and enduring benefits of a simple exercise program, when coupled with behavioral management skills for caregivers, are achievable for AD patients and merit consideration by clinicians. ■

## Spironolactone in Resistant HBP

**Source:** Nishizaka MK, et al. *Am J Hypertens*. 2003;16:925-930.

A COMMONLY ACCEPTED DEFINITION of resistant hypertension (r-HTN) is failure to obtain blood pressure control (ie, < 140/90) with 3 or more different classes of antihypertensive medication. As many as 30% of hypertensive patients may fall into this category; for instance, in the recently completed ALLHAT trial, 34% of subjects, despite intensive multidrug treatment, failed to achieve goal BP.

In the past, use of aldosterone antagonists like spironolactone (SPL) was often reserved for cases of aldosteronism, or in persons plagued with persistent hypokalemia. Doses that may lead to an unacceptable adverse effect profile (100-400 mg/d) were not uncommonly used in such circumstance. Whether more modest doses of SPL (12.5-50 mg/d) might prove effective in r-HTN was the subject of this study.

At 6 months of treatment with SPL, the mean reduction in BP was 25/12 mm Hg. Although subjects who ultimately were determined to have aldosteronism required a higher dose of SPL than persons with low plasma renin, there was no statistically significant difference in efficacy between these subgroups. Similarly, there was no white vs black ethnic disparity in efficacy. The adverse effects profile included 4% incidence of breast tenderness, 7% incidence of worsening renal function, and 3% incidence of hyperkalemia.

It is encouraging that an inexpensive medication (available generically) is generally well tolerated and can provide substantial improvements in BP for persons already on multidrug therapy. ■