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INSIDE

Does Aggressive Surgery Only Benefit Patients with Less Advanced Ovarian Cancer? Results from an International Comparison Within the SCOTROC-1 Trial

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: *Increased PFS associated with optimal surgery is limited to patients with less advanced disease, arguing for case selection rather than aggressive debulking in all patients irrespective of disease extent. Lymphadenectomy may have beneficial effects on PFS in optimally debulked patients.*

Source: Crawford SC, et al. Does Aggressive Surgery Only Benefit Patients With Less Advanced Ovarian Cancer? Results From an International Comparison Within the SCOTROC-1 Trial. *J Clin Oncol.* 2005;23:8802-8811.

THE POSITIVE RELATIONSHIP BETWEEN THE AMOUNT OF SURGICAL residual following primary extirpation of advanced ovarian cancer and survival thereafter has been one frequently cited to justify aggressive surgical evaluation. This bias was initially suggested 3 decades ago and although it has never been proven by a randomized trial, several retrospective, prospective and meta-analyses of clinical trials appear to support the contention. Crawford and colleagues, applying the results from a recently reported randomized controlled clinical trial of post-operative chemotherapy, evaluated this question across a large cohort of ovarian cancer patients with stage IC to IV disease.

The cohorts consisted of 1077 women enrolled in the Scottish Randomized Trial in Ovarian Cancer (SCOTROC-1) trial and randomized to receive combination paclitaxel and carboplatin or doc-

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etaxel and carboplatin following surgery. Women were recruited from centers both within the United Kingdom (UK) and outside the UK. The trial was powered to address a 25% improvement in the median progression-free survival (PFS) for the docetaxel/carboplatin combination. The primary end point, reported previously, demonstrated that median PFS would not be different between the cohorts; thus, it has been widely interpreted that the 2 regimens are equivalent. The primary aim of the current study was to evaluate PFS by surgical outcome, in particular, among patients recruited from within and outside the UK. The premise for this division was based on an observation that less aggressive surgery might be occurring within the UK centers, explaining the disparate survival results observed in these sites compared to other European countries. Three main observations were noted: first, compared to non-UK centers, patients treated within the participating UK sites were significantly less likely to be optimally debulked (≤ 2 cm residual). Second, optimal cytoreduction was associated with an increased PFS; however, the effect was greatest among the patients with less extensive disease at presentation. And third, patients treated within UK sites and with no visible residual disease had a poorer survival than similar residua patients treated outside the UK. This latter observation appeared to be related to the performance of retroperitoneal lymphadenectomy. Crawford et al concluded that the increase in PFS with optimal cytoreduction is limited to patients with less advanced disease at presentation and likely reflects underlying characteristics of tumor biology and that lymphadenectomy may have beneficial effects on PFS in patients without disease residual.

COMMENTARY

The mantra to be aggressive surgically in newly diagnosed advanced staged ovarian cancer patients is a majority consensus throughout the United States and much of the world. Several factors have supported this strategy. First, there are several data sets in the literature that appear to document better outcomes in patients left post-operatively with less residual disease. "Optimal" has been variably defined over the years (by convention it is usually referred to as no individual nodule larger than 1 cm in greatest dimension) but it is hard to accurately estimate. While many have documented that inherent biology may dictate which patients are "debulkable," others have argued that surgical aggressiveness can even overcome this characteristic. Even patients with parenchymal stage IV disease (eg, hepatic metastases) appear to benefit from an aggressive intraperitoneal resection compared to those who are left with bulky intraperitoneal disease. Crawford et al strongly advocate primary surgery for all newly diagnosed patients.

Second, despite the lack of randomized clinical trials, very large data sets subjected to meta-analysis document a near linear relationship between the degree of cytoreduction and survival. However, when studying a cohort of patients deemed "optimal," there is wide variation in survival depending on the amount of disease present

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Questions & Comments

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before attempting cytoreduction. Third, there is a concern that not operating when the diagnosis has been suspected may select a higher proportion of resistant cells ultimately reducing survival. This argument has been advanced against the use of neoadjuvant chemotherapy in patients with advanced disease at presentation.

Fortunately, this issue is being studied in a randomized clinical trial, which should shed light in this contentious area. And fourth, based a recent randomized clinical trial documenting the merits of retroperitoneal lymphadenectomy on PFS, many authors are now advocating systematic surgical evaluation in all patients with advanced disease but particularly in those deemed optimal.[1-3]

Circumstantial evidence abounds, and the current trial appears to fuel the fire. However, there are important nuances brought to light by the SCOTROC-1 trial that have bearing on our enthusiasm for taking an aggressive position. Biology may be important after all. In the current trial, only those patients in the first two quartiles of initial disease volume appeared to benefit from optimal surgery. Currently, studies evaluating the genetic and proteomic signature of patients are underway and preliminarily appear to identify several factors which, if validated, could be used to identify those patients in whom an aggressive surgical attempt should be made and those who are unlikely to benefit from such a procedure. In addition, attention again is directed to the retroperitoneum as a potential haven for metastatic disease. Given the ability to evaluate this area in most patients undergoing surgical extirpation, it is reasonable to add this procedure to those cytoreduced to no visible or minimal visible disease. While a randomized trial would provide the statistical proof necessary to satisfy all in this debate, studies like the current one help to refine the process of providing the appropriate surgery for the appropriate patient with advance ovarian cancer. ■

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Cholesterol Lowering Diet for Pregnant Women May Help Prevent Preterm Birth

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: *A cholesterol-lowering diet may modify maternal lipid levels but not cord and neonatal lipids.*

Source: Khoury J, et al. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. *Am J Obstet Gynecol*. 2005;193:1292-1301.

THERE WAS A RELATIVELY RECENT ARTICLE IN THE *American Journal of Obstetrics and Gynecology* that I passed over the first time, but have decided to cover now since it was highlighted in the *British Medical Journal*.

The concept was to see if eating a healthy diet of low saturated fats and cholesterol would have an effect on maternal, umbilical cord, and 4-day infant blood lipid profiles. In addition, Khoury and associates evaluated various pregnancy outcomes.

In this study, 290 pregnant Norwegian women were randomized to have a *normal* diet (149 patients) or a *modified* diet (141 patients). This latter regimen was heavy on whole grains, fish, fruits and vegetables—yielding a saturated fat intake of less than 8% of total energy and daily cholesterol intake of less than 150 mg/day.

Maternal serum lipid profiles were obtained 4 times during pregnancy. The same lipid analysis was done on cord bloods and neonatal samples at 4 days. The diet regimen had a modest effect on the maternal lipid profile and only late in pregnancy (average total cholesterol of 6.65 mmoL/L vs 6.70 mmoL/L and average LDL of 3.83 mmoL/L vs 3.93 mmoL/L). There was no effect on infant lipid profiles. However, one result should definitely get our attention. The preterm birth rate (< 37 wks) in the modified diet group was 1/141 (0.7%) vs 11/149 (7.4%), which gave a relative risk of 0.10 (95% CI, 0.01-0.77).

■ COMMENTARY

There is not enough space here to go into the num-

bers of articles dealing with various diets, antioxidants, minerals, egg supplements, and herbs that have been postulated to have a beneficial effect on pregnancy outcome. Here is a study to suggest that eating a healthy diet of low saturated fat can possibly decrease the rate of preterm birth, which has risen in the United States from 7.9% in 2003 to 8.1% in 2004 (CDC data), despite current thrusts to decrease it. The knock on the study is that the patient numbers were small. However, the effect on preterm delivery was significant. One wonders whether the results would be even more dramatic if the numbers were increased and the control groups consisted of subjects eating the standard fast food-spiked American diet responsible for our soaring rate of obesity, rather than the "normal" Norwegian diet. ■

BRCA1 and BRCA2 Carriers and Hormone Therapy

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Short-term HRT use does not negate the protective effect of bilateral prophylactic oophorectomy on subsequent breast cancer risk in BRCA1/2 mutation carriers.*

Source: Rebbeck TR, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE study group. *J Clin Oncol.* 2005;23:7804-7810.

REBBECK AND COLLEAGUES IDENTIFIED A COHORT OF 462 women with BRCA1/2 mutations from 13 medical centers in North America and Europe.[1] The incidence of breast cancer was compared in 155 of these women who had undergone bilateral prophylactic oophorectomy with 307 women who did not have the operation. The women who had oophorectomy had a 60% reduction in the risk of developing breast cancer: HR = 0.40 (CI = 0.18-0.92). Hormone therapy of any type did not alter the reduction in breast cancer experienced by the women undergoing oophorectomy. Rebbeck and colleagues concluded that short-term use (several years) of hormone therapy did not have an adverse effect on the beneficial reduction in breast cancer risk following prophylactic oophorectomy.

COMMENTARY

Women with either BRCA1 or BRCA2 germline mutations are advised to undergo bilateral prophylactic oophorectomy after childbearing because approximately 90% will develop breast or ovarian cancer. This surgery reduces the risk of ovarian cancer by about 90% and the risk of breast cancer by about 50%. These relatively young women must consider the postoperative consequences of surgical menopause in their decision-making. This report is the first to provide data on the experience of women undergoing bilateral prophylactic oophorectomy who subsequently used hormone therapy. And the news is good.

Helzlsouer had previously reported that the use of hormone therapy did not adversely affect the reduction of breast cancer observed after prophylactic oophorectomy, but the conclusion was limited by very small numbers.[1] In the current report, 93 (60%) of the women who underwent oophorectomy used hormone therapy. The average length of follow-up was 2.6 years (more than 5 years in 16%) in the surgically treated group and 4.1 years (more than 5 years in 33%) in the non-oophorectomized group. There was no hint of a difference in breast cancer reduction comparing hormone users and nonusers. The findings were similar in 34 women who used a combination of estrogen and progestin, but the power of this finding was limited by the small number.

In their discussion, Rebbeck et al review the reasons to add hysterectomy to bilateral oophorectomy, citing possible adverse effects of progestin treatment and increased risks of uterine, cervical, and fallopian tube cancer in BRCA mutation carriers. The accompanying editorial points out that the data on uterine and cervical cancers are limited by small numbers and not all reports agree. In addition, fallopian tube cancer has not been reported following bilateral prophylactic salpingo-oophorectomy. In those women not willing to undergo prophylactic mastectomy, tamoxifen treatment is offered as preventive therapy. Hysterectomy, of course, removes the possibility of tamoxifen-induced endometrial side effects.

Women who are BRCA carriers face difficult decisions. The experience reported in the PROSE study (Prevention and Observation of Surgical Endpoints) indicates that hormone therapy can be used safely for several years. Continuing follow-up of this cohort may extend this period of safety even longer. The PROSE study has provided new and important information to help BRCA women and their clinicians. It is appropriate for these women to consider hormone therapy as a means to avoid the consequences of surgical menopause. ■

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Laparoscopic Bilateral Salpingo-oophorectomy in Breast Cancer Patients after Transverse Rectus Abdominis Myocutaneous Flap Reconstructive Surgery

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Synopsis: *Laparoscopic RRSO is safe and feasible in patients who have undergone a prior TRAM flap reconstruction.*

Source: Awtrey CS, et al. Laparoscopic bilateral salpingo-oophorectomy in breast cancer patients after transverse rectus abdominis myocutaneous flap reconstructive surgery. *Gynecol Oncol.* 2005;99:720-725.

It has become increasingly documented that removal of the ovaries in high-risk women can not only reduce the risk of gynecologic malignancy but also improve the outcome of women with breast cancer. Resection may be accomplished via laparoscopy or laparotomy; the former is preferred given the reduction in potential complications, shorter recovery, and improved cosmesis. However, laparoscopic removal of the adnexa in breast cancer patients who have had a reconstruction procedure involving a rectus flap can present a challenge both mechanically and anatomically. Awtrey and colleagues reviewed their experience of risk-reducing salpingo-oophorectomy (RRSO) over a 7-year period, dichotomizing the cohort on the basis of whether the procedure was performed in those with rectus muscle reconstruction (TRAM, n = 10) or without reconstruction (n = 92). No differences were noted with respect to patient demographics, body mass index, previous abdominal surgery, menopausal status, or preoperative ultrasound adnexal characteristics. Both cohorts appeared to be similar in operative outcome, post-operative stay, and complications. The only distinguishing variable was the duration of time to completion for those with a history of TRAM reconstruction. Satisfactory operative outcome in relationship to ovarian resection was similar. These data support the feasibility and safety of laparoscopic salpingo-oophorectomy in patients with a history of breast cancer, including those in whom TRAM reconstruction has been performed.

COMMENTARY

The performance of RRSO via laparoscopy has been popular given the accessibility of the adnexa and the benefits of this surgical approach. The procedure is largely performed in the outpatient setting with patients returning to normal activity within a few weeks postoperatively. However, when performing this procedure among patients with a history of breast cancer, special challenges may be encountered, particularly in those undergoing rectus reconstruction. This latter procedure involves migrating the rectus muscle and fascia to the desired location over the chest wall. The resultant defect on the lower abdomen is closed either primarily or with mesh, particularly if a bilateral procedure is undertaken. While the abdominal cavity is rarely violated in this procedure, large non-expandable mesh grafts can preclude abdominal distention—a obvious, desired result for laparoscopic visualization. In addition, the umbilicus, a standard reference point for not only the pelvic brim but also the bifurcation of the aorta, may be misaligned from its natural location.

Both cephalad/caudal and left/right deviations may occur alone or in combination following the procedure. Finally, the transverse incision frequently used for the abdominoplasty may or may not be in an advantageous line for lateral port placement—although that is the desired placement site if possible. For safe and successful laparoscopy, knowledge of these potential situations is critical. Awtrey et al documented in more than 100 patients that the procedure could be safely accomplished in both those with and without TRAM reconstruction. Of the 10 patients with a prior history of TRAM reconstruction, 4 also had synthetic mesh grafts. None of these 10 patients required conversion to laparotomy. This was similar to the rate of conversion observed in patients without reconstruction and similar to the limited experiences of other authors.[1-3] They did record 1 patient in this cohort who had an infection of the mesh prosthesis. A similar rate of wound infection was recorded in the 92 other patients undergoing laparoscopy in non-TRAM cases.

Overall, these data are encouraging and should provide some support for the procedure to those who wish to attempt laparoscopy RRSO. Knowledge of the vascular supply to the umbilicus, location of the umbilicus to the underlying anatomy, reference level of the trans-

verse scar and knowledge of the type of reconstruction performed are critical elements to review prior to attempting the procedure. ■

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Who Uses an Opioid Contract?

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: *Opioid contracts may play an important role in facilitating effective management of patients with chronic pain.*

Source: Touchet BK, et al. Opioid contract use is associated with physician training level and practice specialty. *Journal of Opioid Management*. 2005;September/October:195-200.

FACULTY, RESIDENTS, AND STUDENTS AT THE University of Oklahoma College of Medicine participated in a web-based survey regarding the attitudes toward and prescribing of controlled substances. Opioid contract use was significantly associated with status as a resident rather than student or faculty, primary care specialty, estimated alcohol and illicit drug use by patients, and the perceived risk inherent in prescribing controlled drugs. A majority of participants felt that the use of such a tool increased their sense of mastery and their comfort with prescribing controlled drugs.

■ COMMENTARY

I've chosen an article from a brand new journal because its topic is critically important to the practicing obstetrician/gynecologist. Managing pain is one of the most challenging aspects of any practice of obstetrics and gynecology. Concerns surrounding the use of opioids include fear of causing addiction, potential prescription abuse, and discomfort with dealing with regulatory agencies overseeing the use of controlled drugs. As a result, some practitioners avoid prescribing what otherwise might be very useful medications to a population that is commonly sub-optimally treated.

The opioid contract is poorly studied, but purported to potentially address some of these issues. Contracts between patient and physician are felt to foster improved agreement on treatment approach, patient education, and statement on common goals. They outline terms of the agreement, prohibited behaviors, and conditions for patient dismissal. This particular study is an attempt to look at who uses the contracts within a university system.

It is logical that residents are the most likely to use the contracts within a university setting. Students have little/no authority to write prescriptions, and faculty might tend to rely on their own experience and judgment. It is also logical that primary care physicians are more likely than specialists to use the pain contract since specialists tend to have episodic and short-term relationships with patients whereas the primary care provider has a vested interest in the progression of symptoms and long-term management of pain symptoms.

So where does the practicing obstetrician/gynecologist fit? Where does any physician fit who diagnoses and treats endometriosis, vulvar vestibulitis, interstitial cystitis, pelvic pain, dyspareunia, etc? The answer: right in the middle of it all. Since entering full-time practice, I have been impressed at how often patients are sent to me for ongoing management and/or in consultation because their treating physician is uncomfortable using opioids and controlled drugs. It is the logical extension of having observed residents in training withholding pain medication because of the fear that patients would become addicted or the assumption that any pain was, in fact, a way to seek a prescription for drugs to be abused.

The article refers to a useful website of the American Academy of Pain Medicine and offers a sample pain contract that any office can use. The reader is encouraged to view www.painmed.org/productpub/statements/sample.html. I would suggest that most of us in practice are very much like the resident population in this study. We are volunteer participants in the study because we are interested in treating patients with pain. Since we are not "experts" as faculty at the university but are like the primary care physicians who tend to use the contracts, we can learn from our colleagues and try to

utilize these tools that will help us manage our patients more effectively and efficiently. ■

Maternal Complications with Vaginal Birth After Cesarean Delivery: A Multicenter Study

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Synopsis: *Women with a prior cesarean should be offered VBAC, and women with a prior cesarean and prior vaginal delivery should be encouraged to VBAC. Although other studies have suggested that prostaglandins should be avoided, we suggest that inductions requiring sequential agents be avoided*

Source: Macones GA, et al. Maternal complications with vaginal birth after cesarean delivery: A multicenter study. *Am J Obstet Gynecol*. 2005;193:1656-1662.

THERE ARE MANY FACTORS RESPONSIBLE FOR THE plummeting rate of vaginal birth after cesarean sections (VBACs). However, the major reason for the downward swing is the concern about uterine rupture and its maternal and fetal ramifications.[1-3]

Perhaps the largest study to address the true rate of rupture in VBACs surfaced this November in the *American Journal of Obstetrics and Gynecology* by Macones and colleagues. The lead author is a well-known expert on decision-making analysis.

Macones et al sifted through delivery data from 17 centers during 1996 through 2000. In this study, 25,005 patients were identified who had had previous cesarean sections—11,299 (44%) were sectioned outright and 13,706 (56%) chose to attempt a VBAC. Of the 12,535 patients having had only one prior cesarean section, 9,462 had a successful vaginal delivery (75.5%), while those with two or more prior sections had a similar success rate (878 of 1,171 or 75.0%). The group then assessed the risk of uterine rupture, which was strictly defined as separation of the scar noted at the time of laparotomy in the face of evidence of maternal bleeding or non-reassuring fetal heart tones. Asymptomatic dehiscence was not included as an end point and vertical or unknown scars were excluded.

In a separate spoke of the study, the group analyzed data from the 134 patients with uterine ruptures in comparison with 655 randomly selected non-ruptured controls regarding a variety of clinical and historical factors.

The results were extremely enlightening. First, the overall rupture rate was 9.8/1000, with a rate of 8.7/1000 in those with a single previous cesarean section and 20/1000 in those with 2 or more prior sections. Factors increasing the risk for rupture included the need for induction and/or augmentation, use of prostaglandin and pitocin together, and, as indicated above, more than 1 previous cesarean section. In this study, as opposed to another earlier study, prostaglandin alone did not increase the rate of rupture (but misoprostol was not used in this study). Maternal age, race, or where the patient delivered (tertiary or primary care hospital) had little effect on the results. However, the one factor that had a major decrease in the chances of uterine rupture was a previous successful vaginal delivery. This reduced the risk by 60%, giving an overall theoretical risk of 5.8/1000.

■ COMMENTARY

The very latest data from the CDC from 2004 indicates a cesarean section rate in the United States of 29.1%, up from 20.7% in 1996, the year the above authors began including data in their study. Interestingly, the VBAC rate in the United States in 1996 was 28.3%, but in 2004 it was only 9.2%. Although concern for uterine rupture was the primary reason for this drop, other spin-offs have had a major effect on the trend such as litigious factors, patient inconvenience, fear of labor, and provider inconvenience based on ACOG's admonition that he/she be "immediately available" for all VBAC labors.[4,5]

This large study speaks for itself. The risk of uterine rupture in those having had one previous section is about 1% and, the risk is about 2% in those having had two or more prior sections. Most importantly, those with one prior section and a previous vaginal delivery run a 99.5% chance of no rupture, a risk I would guess almost every woman committed to a vaginal delivery would take—if we would let her. ■

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CME Questions

1. **The following statements are true regarding BRCA carriers and hormone therapy *except*:**
   a. Bilateral prophylactic oophorectomy is highly recommended for BRCA carriers immediately after childbearing.
   b. Bilateral prophylactic oophorectomy only reduces the risk of ovarian cancer in BRCA carriers.
   c. The only available evidence indicates no adverse attenuation by hormone therapy of the benefits associated with bilateral prophylactic oophorectomy.
   d. There is no evidence thus far that estrogen-progestin treatment has a different impact in BRCA carriers than treatment with unopposed estrogen.

Answer: 1(b)

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FDA Recommends Approval of Muraglitazar, But May Need To Reconsider

In September of 2005, an FDA advisory committee recommended approval of muraglitazar for the treatment of type 2 diabetes. However new review of the data presented to the FDA challenges the safety of the drug, and suggests that compared with placebo or standard treatment, muraglitazar is associated with excess mortality.

The drug is a peroxisome proliferator-activated receptor (PPAR) that has both alpha receptor activity (similar to fenofibrate and gemfibrozil) and gamma receptor activity (similar to pioglitazone and rosiglitazone). Muraglitazar has been widely anticipated because of its dual effect of improving lipid profiles and increasing insulin sensitivity in patients with type 2 diabetes.

In the new study, researchers from the Cleveland clinic reviewed the data submitted to the FDA from phase 2 and 3 clinical trials. The combined studies included 3725 patients who were randomized to receive differing doses of muraglitazar, pioglitazone, or placebo in combination with metformin or glyburide in trials ranging from 24 to 104 weeks. The primary end points were death, nonfatal MI, or nonfatal stroke and a more comprehensive composite outcome, which included those 3 outcomes plus incidence of CHF or TIA. The primary outcome (death, MI, or stroke) occurred in 35 of 2374 (1.47%) of muraglitazar treated patients and in 9 of 1351 (0.67%) of patients in the combined placebo and pioglitazone treatment groups (RR 2.23; 95% CI, 1.07-4.66; *P*. = .03). The more comprehensive outcome occurred in 2.11% of muraglitazar treated patients and 0.81% of control patients (RR, 2.62; 95%CI, 1.36-5.05; *P* = .004). Incidence of CHF was 0.55% muraglitazar and 0.07% controls (*P* = .053).

The authors conclude that compared with placebo or pioglitazone, muraglitazar was associated with increased risk of death, major adverse cardiovascular events, and CHF. They also recommend the FDA not approve the drug until safety can be documented (Nissen SE, et al. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes Mellitus. *JAMA*. 2005;294: 2581-2586).

In a related, provocative editorial, James Brophy MD from McGill University suggests tactics that pharmaceutical companies use to "foster an allusion of safety" when presenting data as part of a FDA application including selecting study populations unlikely to have adverse outcomes, conducting under powered studies that are unable to detect meaningful safety differences, reporting individual rather than composite safety outcomes, and others. He poses the question "which safety message will the FDA buy?" (Brophy JM. Selling Safety—Lessons From Muraglitazar. *JAMA*. 2005;294:2633-2635).

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Which Antipsychotics Are More Dangerous?

Newer atypical antipsychotic drugs have been associated with higher death rates in elderly patients. Now, a new study shows that conventional antipsychotics are at least as dangerous as the newer drugs. In a retrospective cohort study, nearly 23,000 patients age 65 and older who had received conventional or atypical antipsychotic medications between 1994 and 2003 were studied. Conventional antipsychotic medications were associated with a significantly higher adjusted death rate then atypical antipsychotic medications for all time intervals studied up to 180 days (relative risk 1.37; 95% CI, 1.27-1.49). The relative risk was also higher for less than 40 days (RR, 1.56), 40-79 days (RR, 1.37), and 80-180 days (RR, 1.27). The greatest risks were for death occurring within the first few weeks after initiation of medication especially higher doses of conventional antipsychotics drugs.

The authors conclude that conventional antipsychotic medications are least as likely as atypical agents to increase the risk of death among elderly patients, and that conventional drugs should not be used to replace atypical agents if they were discontinued because of recent FDA warnings (Wang PS, et al. Risk of Death in Elderly Users of Conventional Vs. Atypical Antipsychotic Medications. *N Engl J Med*. 2005;353:2335-2341).

Should CPOE Undergo Evaluation?

Physicians who use computerized physician order entry (CPOE) systems often report that it is not a panacea for saving time and preventing medication errors. A new study raises concerns about an increase in adverse outcomes associated with CPOE. Researchers from Children's Hospital of Pittsburgh reviewed demographic, clinical, and mortality data before and after implementation of a commercially sold CPOE. Mortality rates were significant higher after implementation (75 deaths among 1942 children, 3.86% after implementation vs 39 of 1394, 2.80% prior to implementation, odds ratio: 3.28; 95% CI; 1.94-5.55). The authors suggest that while CPOE may hold great promise, "Institutions should continue to evaluate mortality effects, in addition to medication air rates. . ." They also suggest that CPOE should undergo rigorous review and evaluation, similar to drugs, to assess safety prior to implementation (Han YY, et al. Unexpected Increased Mortality After Implementation of a Commercially Sold Computerized Physician Order Entry System. *Pediatrics*. 2005;116:1506-1512).

New Treatment for Tennis Elbow

Botulinum toxin may be effective for treating tennis elbow, according to new study. Sixty patients with lateral epicondylitis were randomized to injections of 6 units of botulinum toxin type A or normal saline placebo injections. Subjective pain was significantly reduced in the botulinum group at 4 weeks (visual analog scale 25.3 mm botulinum vs 50.5 mm placebo [$P < 0.001$]) and was sustained at 12 weeks. Grip strength was not statistically different between the 2 groups, although mild paresis of the fingers occurred in 4 patients in the botulinum group at 4 weeks, but none of the patients in the placebo group. In only one patient did the symptoms persist until week 12. More patients in the botulinum group experience weak finger extension at 4 weeks as well (10 patients botulinum vs 6 patients placebo).

The authors conclude that botulinum toxin may be effective in treating pain over 3-month periods in patients with lateral epicondylitis, but the injections may be assisted with digit paresis and weakness of finger extension (Wong SM, et al. Treatment of Lateral Epicondylitis with Botulinum Toxin: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Int Med*. 2005;143: 793-797).

FDA Actions

Moxifloxacin (Avelox-Bayer) has been approved for the treatment of complicated intra-abdominal infections including polymicrobial infections. The approval was based on a study which showed that intravenous or oral moxifloxacin was as effective as IV therapies such as piperacillin/tazobactam (Zosyn) followed by oral amoxicillin/clavulanic acid (Augmentin). In a separate study, moxifloxacin was found to be equivalent to ceftriaxone plus metronidazole followed by oral amoxicillin/clavulanic acid for treating complicated intraabdominal infections. Moxifloxacin is also approved for treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, and skin and skin structure infections caused by susceptible organisms. ■