



# AMERICAN COLLEGE OF SURGEONS

## SURGERY NEWS

### FDA Begins Quarterly Posting of Drug Safety Information

BY ELIZABETH MEHCATIE  
Elsevier Global Medical News

The Food and Drug Administration has posted on its Web site the first quarterly report of drugs identified as having “potential safety issues” that are under evaluation, in order to keep health care professionals and the public informed about latest drug safety information available, the agency announced in September.

A drug will be placed on the list when a review of reports to the FDA’s Adverse Event Reporting System (AERS) indicates that it may be associated with a potential safety issue and is under investigation by the agency. But inclusion on the list “does not mean that FDA has concluded that the drug has the listed risk or that FDA has identified a causal relationship between the drug and the listed risk,” according to an FDA statement, which also says that the appearance of a drug on the list “does not mean that FDA is suggesting that [health care] providers should not prescribe the drug or that patients taking the drug should stop taking the medication.”

The process of identifying potential safety issues from AERS reports and investigating those issues already is part of the postmarketing safety review of drugs. Now the news that such an investigation is underway is being made available to the public at an early stage.

The inaugural report lists 20 drugs that were identified as having a potential safety issue from January through March 2008. The potential safety signals on the list range from dosing confusion with insulin U-500 (Humulin R) and overdoses caused by confusion over package labels on quetiapine (Seroquel) samples, to anaphylactic-type reactions with heparin and purple glove syndrome with intravenous phenytoin injection (Dilantin). Other drugs on the list include duloxetine (Cymbalta), under investigation for reports of urinary retention; octreotide acetate depot (Sandostatin LAR), under investigation for reports of ileus; and desflurane (Suprane), under investigation for reports of cardiac arrest.

Upon completion of evaluation of a drug’s potential safety issue, the FDA may

update the label, institute risk management program or other regulatory actions, or, in some cases, when the suspected association is determined to be not related to the drug, take no further action. Dr. Gerald Dal Pan, director of the Office of Surveillance and Epidemiology at the FDA’s Center for Drug Evaluation and Research, said during a press briefing. For example, last year, omeprazole (Prilosec) and esomeprazole (Nexium) were reviewed after a study indicated they may be associated with an increase in MIs, but no such association was found.

He acknowledged that consumers could misinterpret why the drug is on the list and might stop taking a drug when cessation is not indicated, but he emphasized that the placement of a drug on the list is an indication that, “we have simply received an adverse report or reports and we’re trying to assess the potential association between that adverse event and the drug.”

People taking one of the drugs listed who experience an adverse event should be encouraged to inform their health care

providers, who in turn should be encouraged to report the event to the AERS, which “will help us in evaluating that potential association,” Dr. Dal Pan said.

The posting of this list is required under the FDA Amendments Act of 2007, which requires that the agency provide the public with any new safety information or “potential signals of serious risk” that have been identified from the review of the adverse event reports submitted to AERS, which it receives from health care professionals, patients, and pharmaceutical companies. The AERS database contains about 4 million reports of potential drug reactions for marketed products and receives several hundred thousand such reports yearly.

The list is available at [www.fda.gov/cder/aers/potential\\_signals/potential\\_signals\\_2008Q.htm](http://www.fda.gov/cder/aers/potential_signals/potential_signals_2008Q.htm).

Serious or unexpected adverse events associated with drugs can be reported to the FDA MedWatch program at 800-332-1088 or [www.fda.gov/MedWatch/report.htm](http://www.fda.gov/MedWatch/report.htm).

### Fundoplication Best Tames GERD Over the Long Term

BY JEFF EVANS  
Elsevier Global Medical News

PHILADELPHIA — Laparoscopic Nissen fundoplication appears to offer better overall control of gastroesophageal reflux disease symptoms than does optimized medical therapy for patients who are stable and symptomatically controlled on long-term medical therapy, according to a randomized study of 101 patients.

At 3 years after the start of the trial, surgical patients generally had more symptom-free days, greater satisfaction with their control of symptoms, less esophageal acid exposure, and better quality of life than did patients who received optimal proton-pump inhibitor (PPI) therapy throughout the trial, Dr. Mehran Anvari reported at the annual meeting of the Society of American Gastrointestinal and Endoscopic Surgeons.

At least five randomized, controlled trials of surgical vs. medical intervention for gastroesophageal reflux disease (GERD) have been published in the last 15 years. Although surgery was reported to have superior outcomes to medical therapy in each trial, “there is still considerable debate as to the relative role of surgery in treating patients with chronic medical therapy, to the point that, over the last 2 years, a number of treatment algorithms that have been published by major GI centers in a major GI journals have not even included surgery as an option for patients on long-term medical therapy,” said Dr. Anvari, director of the Centre for Minimal Access Surgery at McMaster University, Hamilton, Ont.

Problems with those clinical trials included the use of

mixed patient populations, lack of optimization of medical therapy based on current standards, mixed types of surgical procedures, and selective follow-up, often using subjective rather than objective parameters.

The report of an 11-year follow-up of one of these trials (N. Engl. J. Med. 1992;326:786-92) fueled the debate further by suggesting that the results of surgery—in this case, open Nissen fundoplication—were short-lived (JAMA 2001;285:2331-8).



**Satisfaction with symptom control was 15% higher in surgical patients than in patients on medical therapy.**  
DR. ANVARI

In a randomized, nonblinded study, Dr. Anvari and his coinvestigators compared the 3-year results of 101 patients who underwent either laparoscopic Nissen fundoplication or optimized PPI therapy.

The patients in the investigation had controlled their GERD symptoms with PPIs but still required long-term PPI therapy. All patients had been taking PPIs continuously for at least 1 year and had good symptom control—a GERD symptom scale (GSS) score of less than 18 on a range of 0-60 and a visual analog scale score of greater than 70 (which is considered to be adequate for satisfaction with symptom control) on a range of 1-100.

The operations were done by four surgeons who each had performed more than 50 laparoscopic Nissen fundoplication procedures. Surgical patients discontinued their use of PPIs after their operation.

Patients randomized to medical therapy received treatment using a standardized management protocol based on best evidence and published guidelines.

The average GSS scores were similar in both groups at 1 and 3 years. At 3 years, the 51 patients randomized to surgery had an average of nearly seven symptom-free days

per week, compared with about six per week in the 50 patients randomized to medical therapy. Unlike medical therapy, surgery was associated with normalization of lower esophageal sphincter pressure.

On 24-hour pH monitoring at 3 years, surgical patients spent a mean of 2% of the duration of monitoring with a distal esophageal pH less than 4, but patients on medical therapy spent more than 4% of the duration with a pH below 4 even though they remained on PPIs. However, each group had a similar drop in the percentage of time spent at a pH less than 4.

At 3 years, satisfaction with symptom control was 15% higher in surgical patients than it was in patients on medical therapy. Although both treatments helped patients maintain a high quality of life as measured on the Short Form-36 questionnaire, surgery was superior to medical therapy in improving quality of life, said Dr. Anvari, professor of general surgery at the university.

Treatment failures occurred in 18% of surgical patients (three patients required revisions because of persistent dysphagia, and six needed PPI therapy) and in 16% of patients on medical therapy (eight required surgery).

The surgical patients stayed an average of 2.8 days in the hospital. There were no conversions to open surgery or major intraoperative complications, but four patients had persistent bloating.

“Laparoscopic Nissen fundoplication should be offered to those patients requiring more than 2 years of PPI therapy who are seeking alternatives. And it should be a standard for comparison [against] all endoscopic antireflux procedures that are currently being devised,” Dr. Anvari advised. He reported no relevant conflicts of interest and said there was no industry involvement in the conduct of the study.

# Trinkets Out, 'Educational' Gifts OK Under New Code

BY MARY ELLEN SCHNEIDER  
Elsevier Global Medical News

The free pens and mugs adorned with the names of commonly prescribed drugs are soon to be a thing of the past, thanks to a new set of voluntary guidelines from the Pharmaceutical Research and Manufacturers of America.

But the real impact of the guidelines is still up for debate.

The voluntary guidelines, an update of the 2002 PhRMA Code on Interactions with Healthcare Professionals, will go into effect in January 2009.

"Although our member companies have long been committed to responsible marketing of the life-enhancing and life-saving medicines they develop, we have heard the voices of policymakers, health care professionals, and others telling us we can do better," Billy Tauzin, PhRMA president and CEO, said in a statement.

Among the changes outlined in the new guidelines is a prohibition on even "modest" gifts to physicians if they lack

educational value, such as the ubiquitous pens and mugs. However, gifts valued at \$100 or less that are used primarily for patient or health care professional education, such as an anatomical model, are still allowed on an occasional basis.

The guidelines also prohibit sales representatives and their immediate managers from taking physicians out for dinner, even if they have an educational presentation to make. However, they may provide "modest" meals, such as pizza, in the office or at the hospital if they stay to provide their educational session there. Providing any type of entertainment or recreational items such as tickets, sports equipment, or trips is prohibited.

The guidelines call on pharmaceutical companies to separate their continuing medical education (CME) grant-making functions from their sales and marketing activities. Subsidies to attend CME meetings should not be given directly to physicians; instead, any funds should be given directly to the CME provider who can use the money to reduce fees for all attendees.

Companies are also not allowed to provide meals directly at CME events.

The guidelines continue to allow pharmaceutical companies to provide scholarships to medical students and others in training so they can attend educational conferences, as long as the recipients are chosen by the academic or training institution.

The guidelines also call for greater transparency among physicians who work as industry consultants. Physicians who serve as company consultants or speakers and also serve on committees that set formularies or clinical practice guidelines should disclose their industry relationships, according to the PhRMA guidelines.

## Changes Provoke Praise, Skepticism

While the PhRMA guidelines don't go as far as some academic medical institution policies, they are significant because they appear to have the full backing of the industry, said Dr. David Korn, chief scientific officer for the Association of American Medical Colleges, which recently released its own report on industry funding of med-

ical education. It shows that the pharmaceutical industry has heard the public's concerns and has deemed some interactions to be unacceptable. "What we're talking about really is a culture change," he said.

In the AAMC report, released in June, the organization calls on medical schools and teaching hospitals to prohibit the acceptance of any gifts from industry. The AAMC also instructs academic medical institutions to set up a central CME office to coordinate the distribution of industry funds, and strongly discourages participation by faculty in industry-sponsored speakers bureaus.

Time will tell whether the guidelines will result in any real changes, said Dr. Howard Brody, director of the Institute for the Medical Humanities at the University of Texas Medical Branch in Galveston.

All physicians should start thinking about how to get educated about new treatments without meeting with sales representatives, foregoing samples, and saying no to free lunches provided by pharmaceutical companies, he said. ■

## Overdoses of Illicit Fentanyl Claim 1,000 Lives in 2 Years

BY ALICIA AULT  
Elsevier Global Medical News

At least 1,000 people died in a 2-year period from an overdose of an illegally manufactured nonpharmaceutical fentanyl that hit the streets sometime in 2006, according to a survey of U.S. surveillance data.

It is the largest-ever reported epidemic related to overdose of non-pharmaceutical fentanyl (NPF), said the authors of a report in *Morbidity and Mortality Weekly Report*, published by the Centers for Disease Control and Prevention.

The CDC began ad hoc case-finding and surveillance following reports of increases of overdoses in 2006 in Camden, N.J.; Maryland; Chicago; Detroit; and Philadelphia. Initially, the overdoses were attributed to heroin, but autopsies and law enforcement evidence implicated NPF.

The Drug Enforcement Administration (DEA) took over the CDC monitoring effort, which involved collaborations with medical examiners, law enforcement, and public health departments in six states and localities: all of Delaware and New Jersey; Cook County, Ill.; Wayne County, Mich.; St. Louis and St. Louis County; and Philadelphia.

From April 2005 to March 2007, there were 1,013 deaths in those areas attributable to illicit NPF (MMWR 2008;57:793-6). Outside of this formal tally, there were also reports of deaths elsewhere in Illinois, Michigan, and Pennsylvania, and in Maine, Maryland, Massachusetts, New Hampshire, Ohio, and Virginia, said the authors, who represented medical

examiners, health departments, and substance abuse officials from the six monitored jurisdictions.

In most of the cases, the NPF was mixed with heroin or cocaine. NPF is 30-50 times more potent than heroin, according to the DEA. Mortality peaked in June 2006, with 150 cases. By spring 2007, the death rate had dwindled, with one death in February and one in March.

Age, sex, and race were known for 984 of those who died. Half of the

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victims were aged 35-54 years, and 80% were men. Slightly more than half were white, 40% were black, and 4% were Hispanic.

In response to the epidemic, public health officials warned physicians, law enforcement, and drug users. The DEA and other law enforcement agencies targeted manufacturers, sellers, and distributors. One factory in Toluca, Mexico, was shut down in May 2006; and in April 2007, the DEA began strictly regulating access to *N*-phenethyl-4-piperidone, a chemical used to make NPF.

The outbreak indicates a need to improve identification and reporting of drug-related deaths to enable a faster public health and law enforcement response, wrote the authors. ■

## Fibrinolysis Tops VATS in Children With Empyema

BY MICHELE G. SULLIVAN  
Elsevier Global Medical News

PHOENIX — Fibrinolysis is about two-thirds the price, but just as effective as video-assisted thoracoscopic surgery for children with empyema, based on a study of 36 patients younger than 18 years.

The outcome of the study surprised Dr. Shawn St. Peter, who was betting on the surgical approach going into the prospective randomized trial. But there is no doubt now, he said, that fibrinolysis should be the treatment of choice for these children, with video-assisted thoracoscopic surgery (VATS) reserved for those who fail medical therapy.

"I can stand here with a bit of clinical humility but with scientific confidence and tell you that patients with empyema should first have a chest tube placed and a fibrinolytic agent infused. Once the drainage has stopped, if they're not getting better, do a repeat imaging. If they have consistent disease, then we should go to VATS," he said at the annual meeting of the American Pediatric Surgical Association.

Dr. St. Peter, director of the University of Missouri-Kansas City center for prospective clinical trials, randomized the 36 young patients to either fibrinolysis or VATS. Children in the fibrinolysis group had a 12-French chest tube placed, followed by an infusion of 4 mg of tissue plasminogen activator (TPA) mixed with 40 mL of normal saline. The infusion was repeated twice, once at 24 hours and again at 48 hours. The VATS group underwent standard thoracoscopic debridement.

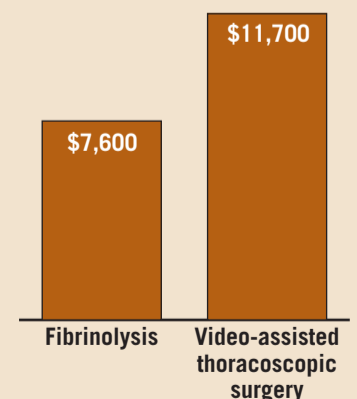
There were no significant differences on any of the primary or secondary clinical outcomes, Dr. St. Peter noted. Length of stay was a mean 7 days in each group. Each group had a mean 2 days of posttreatment oxygen support. The VATS group became afebrile a mean

3 days after the surgery, while the fibrinolysis group took almost a mean 4 days to become afebrile, but the difference was not significant. Children in each group required a mean 22 analgesia doses. Three children failed fibrinolytic therapy and then underwent VATS.

VATS cost a mean of \$11,700, while the mean cost of fibrinolysis was \$7,600, a significant difference.

During the enrollment period of this study, a London-based group published the results of a similar trial. Dr. Samatha Sonnappa and colleagues randomized 60 children to VATS or fibrinolysis with urokinase (*Am. J. Resp. Crit. Care* 2006;174:221-7). They found no significant difference in length of stay after intervention, total hospital stay, failure rate, or radiologic outcome at 6 months after intervention. The mean cost of fibrinolysis was \$9,127, significantly lower than the mean cost for VATS of \$11,379. ■

### Mean Procedural Costs for Empyema Treatment in Children



Note: Based on a randomized study of 36 children.  
Source: Dr. St. Peter

# Minimally Invasive Adrenalectomy Reaches U.S.

BY BRUCE JANCIN

Elsevier Global Medical News

NEW YORK — Posterior retroperitoneoscopic adrenalectomy is a safe and attractive option for minimally invasive removal of benign adrenal tumors and isolated adrenal metastases, according to the experience of surgeons at the University of Texas M.D. Anderson Cancer Center, Houston.

In the first 62 patients at the center to have adrenal glands removed via the posterior procedure, the average operative time was 2 hours for unilateral cases, with a median hospital stay of 2 days. The procedure proved especially useful for patients who had extensive abdominal adhesions from prior surgery, as well as for those undergoing bilateral adrenalectomy. Outcomes for obese patients were as good as for the rest of the group.

The posterior procedure “has become our routine practice and our approach of choice in the majority of patients who require adrenalectomy,” Dr. Nancy D. Perrier of M.D. Anderson said at the annual meeting of the American Surgical Association.

Outside of M.D. Anderson, the operation is not often done in the United States. Its leading proponent is Dr. Martin K. Walz of the University of Essen (Germany). Three endocrine surgeons from M.D. Anderson who saw Dr. Walz’s presentation in New York City of his 560-procedure, 520-patient series were so impressed that they traveled to Germany to learn his techniques. In his series, the mean operating time was 67 minutes, blood loss was 10 mL, and the major complication rate was 1.3% (Surgery 2006;140:943-8). The surgeons then brought him to Houston to provide further guidance.

Dr. Walz, a surgical innovator, introduced two major advances in posterior retroperitoneoscopic adrenalectomy. He established the safety of using CO<sub>2</sub> insufflation pres-

ures that are double the usual 10-12 mm Hg used in abdominal procedures; these pressures create a much larger space for dissection, and make for excellent visualization by essentially eliminating venous bleeding. He also showed that freeing the gland from the kidney as an early step, and leaving the adrenal hanging from its superior attachment, made dissection of the gland easier and safer, said Dr. Perrier, an endocrine surgeon at M.D. Anderson.

Patient positioning is key to the procedure. The patient is put to sleep in the supine position, then turned to a prone jackknife position atop a ventral rectangular support on the operating table to allow for maximum distention between the 12th rib and iliac crest. This lets the abdominal wall contents hang freely, permitting a significant amount of insufflation without negative pressure. A 10-mm port is placed below the tip of the 12th rib, a second one is placed medially, and a 5-mm trocar is placed laterally.



**The posterior procedure has become our routine practice in most adrenalectomy patients.**  
DR. PERRIER

The next important part of the operation is to obtain familiar anatomic landmarks, including the superior pole of the kidney, the inferior vena cava, and the blue-hued liver.

Then comes the critical move: elevating the inferior pole of the adrenal off of the superior pole of the kidney as it is retracted inferiorly; this allows the gland to suspend from the retroperitoneal fibrous adhesions, permitting its easy dissection, the surgeon continued.

Dr. Perrier, an ACS Fellow, reported on the first 68 adrenal glands removed from 62 patients via posterior retroperitoneoscopic adrenalectomy at M.D. Anderson. Thirty-three were unilateral procedures. Most of the patients had pheochromocytomas. One-quarter had metastatic lesions, mostly from the lung. Thirty-four patients had extensive adhesions from prior abdominal operations, so the transabdominal approach was contraindicated.

The mean tumor size was 3.3 cm. The Houston group will not use posterior retroperitoneoscopic adrenalectomy for tumors larger than 6 cm because the prevalence

of primary malignancy in such tumors is at least 25%.

The mean operative time was 2 hours for unilateral cases, with a median 2-day hospital day. There were 11 complications, consisting of 6 intraoperative conversions and 5 postoperative complications, including acute respiratory distress and retroperitoneal hematoma. Results among patients in the first half of the series were similar to those in the second half.

Dr. Quan-Yang Duh, an ACS Fellow, commented that although he adopted transabdominal laparoscopic adrenalectomy as his standard approach in the 1990s, he has long thought that posterior retroperitoneoscopic adrenalectomy sounded more attractive for patients with extensive abdominal adhesions from prior surgery and for those requiring bilateral adrenalectomy.

But it’s a complex operation. The anatomy can be confusing because of the unfamiliar posterior approach. How difficult is it to teach this operation to trainees? asked Dr. Duh, professor of surgery at the University of California, San Francisco.

Dr. Perrier replied that she and her colleagues believe posterior retroperitoneoscopic adrenalectomy is best left in the hands of endocrine surgeons, who will be making the procedure a substantial part of their careers. A general surgeon who might perform only one or two per year will not be able to become facile at it, so she is not teaching it to them.

Dr. Richard A. Prinz said the posterior approach should be used with caution in patients with extensive retroperitoneal fat. “One size does not fit all when it comes to removal of the adrenal from retroperitoneal tissues,” said Dr. Prinz, chairman of the surgery department at Rush University Medical Center, Chicago, and an ACS Fellow.

Dr. Perrier agreed that it’s best not to begin with patients who have extensive retroperitoneal fat; however, 27 of the 62 patients in her series were obese, and their outcomes were as good as were those of other patients.

She stressed that the posterior approach has no role when adrenocortical carcinoma cannot be ruled out preoperatively. Those tumors require open surgery. ■

## Surgical Dogma Challenged on R1 Liver Resection

BY BRUCE JANCIN

Elsevier Global Medical News

NEW YORK — The traditional dogma that R1 resection of colorectal cancer metastases to the liver is an absolute contraindication to surgery should be discarded, Dr. René Adam asserted at the annual meeting of the American Surgical Association.

With contemporary, more effective chemotherapy and improved surgical techniques, 5-year survival following an R1 resection—that is, complete macroscopic tumor resection but with positive margins—is similar to that of R0 resection as defined by negative margins, according to Dr. Adam of Paul Brousse Hospital, Villejuif, France.

An R0 liver resection remains the preferred method, but it’s not always possible because of tumor multinodularity or vascular proximity.

“Should R1 resection by necessity be considered as a contraindication to surgery? Certainly yes. What’s the alternative: the absence of surgery? We know that with the absence of surgery, there is

almost no possibility of 5-year survival, even with aggressive chemotherapy. Our 57% 5-year survival [with R1 resection] is a significant benefit,” he said.

R1 resection by necessity is permitted at the French hospital. Dr. Adam presented a comparison of outcomes in 202 patients



**Five-year overall and disease-free survival rates were similar in the R1 and R0 resection groups.**  
DR. ADAM

with colorectal metastases only to the liver who received R1 resection and 234 patients who underwent R0 resection. The two groups differed in that those with an R1 resection were younger, had a higher rate of multilobular disease, had more and larger metastases, and were more likely to get pre- and postoperative chemotherapy.

The 5-year intrahepatic recurrence rate was significantly higher in the R1 group, but the extrahepatic recurrence rate was lower. However, these liver recurrences were success-

fully managed by an aggressive regimen of chemotherapy and repeat surgery, as evidenced by the fact that 5-year overall and disease-free survival rates were similar in the R1 and R0 groups (see box).

Dr. Adam surmised that coagulation of the remnant transection to achieve hemo-

stasis might provide a stable 1- to 2-mm buffer zone in R1 patients that helps dampen their risk of recurrence despite the positive margins.

“And when there is a recurrence, repeat surgery is associated with good survival. Survival after the second and third hepatectomy is similar to that after the first,” he observed.

Discussant Dr. Michael A. Choti, an ACS Fellow and professor of surgery at Johns Hopkins University, Baltimore, thanked Dr. Adam for “an outstanding

contribution to the field” that challenges the necessity to achieve negative margins.

He was particularly intrigued by Dr. Adam’s notion that use of the ultrasonic dissector and argon beam coagulation might create a barrier to the spread of residual tumor cells.

Dr. Choti noted that newer thermal coagulative devices are capable of achieving even deeper ablation of the resection margin. He speculated that these tools might reduce the risk of recurrence even further. ■

### Patient Characteristics and Key Outcomes

	R0 patients (n = 234)	R1 patients (n = 202)
Three or more liver metastases at diagnosis	26%	44%
Preoperative chemotherapy	67%	81%
Hepatectomy involving three or more segments	41%	57%
Postoperative chemotherapy	78%	88%
Intrahepatic recurrence	17%	28%
Extrahepatic recurrence	48%	31%
Repeat hepatectomy	23%	23%
5-Year overall survival	61%	57%
5-Year disease-free survival	29%	20%

Source: Dr. Adam