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Critical Care [ALERT]

A monthly update of developments in critical care and intensive care medicine

SPECIAL FEATURE

Update on Drowning

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Dr. Akhtar reports no financial relationship to this field of study.

INTRODUCTION AND EPIDEMIOLOGY

Drowning is defined as asphyxia or suffocation from submersion/immersion in a liquid medium. Tissue oxygen deprivation is what leads to organ injury and death. Drowning also has been defined as death by asphyxia within 24 hours of submersion with terms such as near-drowning, secondary drowning, submersion injury, and immersion syndrome used for longer survival after submersion or other clinical circumstances; current guidelines recommend simply using the term drowning.[1]

Drowning is a common and usually preventable cause of considerable morbidity and mortality in pediatric and adult populations. It is the sixth leading cause of accidental death in persons of all ages in the United States (and the second leading cause of death for those aged 1-14 years), resulting in 3939 deaths in 2007. It is the fourth leading cause of death worldwide with more than 300,000 deaths yearly.[2,3]

The incidence of near-drowning (i.e., survival after drowning) is not as well known (since many cases are never reported) but is estimated to be several-fold greater than that of drowning with some authors estimating as many as 70,000 persons affected yearly in the United States. Of these, it has been observed that about 10%-25% die; of the survivors, 10% are left with neurological deficits and the remainder survive intact.[4]

Drowning is most common in children (usually in the home environment) and young adults (age 15-25 years, usually in lakes or rivers). The bulk (> 90%) of drownings occur in fresh water. The majority of episodes of drowning involve males; African American and Native American persons are at higher risk than Caucasians. Alcohol is a

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factor in about 50% of cases.[2,5]

Risk factors for drowning include alcohol or drug use, poor swimming skills and, for children, lack of adult supervision. Presence of an underlying seizure disorder (increases risk of drowning in children by > 10-fold), hyperventilation prior to swimming or occurrence of concomitant trauma, acute myocardial infarction, acute stroke, or arrhythmia may lead to drowning (15% of syncopal events related to long QT syndrome occur during swimming).[6-8]

PATHOPHYSIOLOGY AND PRESENTATION

Hypoxia is the common denominator of the pathophysiology of drowning. The initial response to submersion is breath holding and panic/struggle to rise to the surface, for up to a few minutes. Ultimately the victim takes an involuntary breath and water enters the hypopharynx, leading to laryngospasm. Sustained laryngospasm occurs in < 10%-15% of victims (formerly termed "dry drowning"), while glottic relaxation occurs in the majority of persons ("wet drowning") and results in more significant lung injury. There may be vomiting and aspiration of gastric contents as well. Ongoing hypoxemia then leads to brain and myocardial injury, circulatory collapse, other end-organ ischemia, and ultimately, death.[6,9]

More specifically, from a pulmonary standpoint, aspiration of water results in disruption of surfactant, alveolar collapse, and atelectasis. Alveolar-capillary damage from aspiration causes capillary leak and pulmonary edema; there also may be a component of cardiogenic or neurogenic pulmonary edema. Small airways may be obstructed by aspirated water, debris, or gastric material and there may be bronchospasm. Risk of acute lung injury in the setting of drowning is estimated to be as high as 40%.[4,6,10]

Historically, it was believed that due to osmotic shifts, salt water drownings were associated with greater pulmonary edema — and perhaps relative hypovolemia — while fresh water drownings carried a higher risk of hypervolemia and electrolyte abnormalities such as hyponatremia. Experience has shown that although there may be some theoretical differences between salt water and fresh water aspiration, these are rarely clinically significant.[11]

From a cardiac standpoint, victims of drowning may have evidence of shock with reduced cardiac function. Hypoxemia and hypothermia predispose to arrhythmias (most commonly bradycardia). Cold diuresis may also lead to relative hypovolemia and hemodynamic instability.[4,6]

Neurologically, diffuse neuronal damage and loss of blood-brain barrier occur resulting in cerebral edema. In the normothermic patient, full and normal neurologic recovery may be possible at 5-7 minutes of anoxia but is unlikely with greater periods of anoxia; this interval can be several-fold higher in the hypothermic patient. Finally, unless the drowning was known to have been high-impact or in a high-risk setting, the likelihood of cervical spine injury is quite low at < 1% in one large study of more than 1000 patients.[12]

Metabolic acidosis (lactic acidosis from initial muscle overuse and fatigue while struggling and then hypoxia/hypoperfusion of tissues), respiratory acidosis (related to apnea), acute tubular necrosis, and small transient changes/abnormalities in electrolytes may occur. Rarely, hemolysis and diffuse intravascular coagulation are also seen.

The clinical presentation of drowning varies widely with victims being asymptomatic to obtunded. Cough, dyspnea, and tachypnea are common presenting symptoms and signs. Chest x-ray is normal in about a fifth of patients; pulmonary edema and atelectasis are the usual findings in the rest.

MANAGEMENT

Historically, there have been some unusual approaches to resuscitation and

treatment of victims of near-drowning, including "insufflation of smoke of tobacco into the rectum," slinging persons in prone position on a horse, or placing victims on a tilting board to move the diaphragm.[4] These are no longer practiced.

The first steps in managing a drowning victim are to remove him or her from the water and, if indicated, initiate CPR and ACLS protocol; obtaining a history of events also is essential. Rescue breathing should begin even while in the water. Caution should be used with manipulating the neck in case of cervical spine/cord injuries but, as discussed above, unless a high-risk/high-impact event clearly took place, the risk of spinal cord injury in most drownings is small and routine stabilization of the C-spine after drowning is not necessary.[1]

Once the victim is out of the water, wet clothing should be removed and the person covered/warmed with dry blankets. Rewarming is recommended for those with core body temperature < 34°C. CPR and resuscitation should not be stopped until body temperature is at least > 32°C; good neurological outcomes have been reported for resuscitation after prolonged cold-water submersion. Although reported in small studies with variable outcomes, maintenance or induction of hypothermia is not recommended at this time for victims of drowning. Neither are corticosteroids or barbiturates (considered in the past for prevention or limitation of cerebral edema in drowning).[6,13]

Application of the Heimlich maneuver or any attempted postural drainage of water is not recommended; these measures do not aid in removal of lung water, may precipitate aspiration, and can delay initiation of effective therapies.[4]

In the emergency room and hospital, full evaluation for trauma/other injury is indicated. Airway protection with intubation and provision of ventilatory support must be considered. IV fluid support should be provided, typically without glucose. (The recommendation to avoid hyperglycemia in victims of drowning is based on data from outcomes in patients with ischemic stroke, animal models of drowning, and some retrospective studies of pediatric drowning that suggest worse outcome with hyperglycemia.)

Routine antibiotic prophylaxis is not recommended; antibiotics should only be considered for persons who are submersed in grossly contaminated water. There are multiple case reports of pneumonia after drowning with *Aeromonas*, *Pseudomonas*, *Aspergillus*, *Pseudallescheria*, and others.[14]

Finally, although there are case reports of use of exogenous surfactant for victims of drowning, surfactant is not recommended as standard therapy for lung injury or hypoxia from drowning.[15]

OUTCOME

Overall survival after drowning is 75%-90% with the majority of patients having normal neurological outcome (75%-80%). Although several predictive scoring systems have been proposed and tested in limited trials (Orlowski, Conn-Modell, Graf and others), none have performed consistently or been incorporated into standard clinical practice. Not surprisingly, clinical course and neurological exam over the first 24-72 hours are the best predictors of outcome. Submersion time < 10 minutes, younger age, and mild hypothermia at presentation are predictors of improved survival. Time to initiation of CPR, duration of resuscitation, initial GSC < 5, fixed dilated pupils, asystole on arrival to hospital, and initial arterial pH < 7.1 are associated with poor survival.[8,16]

CONCLUSION

Drowning is an avoidable injury that causes significant morbidity and mortality. Hypoxia leads to end-organ injury with the lungs and brain most commonly and severely impacted. The treatment is standard aggressive resuscitation including effective CPR, correction of hypothermia, volume support, appropriate low tidal volume ventilation for acute lung injury, and other usual supportive care.

Prevention is key. Some effective measures are: public education on water safety and CPR, good swimming skills, avoidance of alcohol/drugs when engaged in water activities, supervision for children or poor swimmers, and swimming with another person particularly if there is a history of seizures or syncope. ■

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ABSTRACT & COMMENTARY

The Impact of Establishing a Regional Weaning Unit for Patients Requiring Prolonged Mechanical Ventilation

By Richard J. Wall, MD, MPH

Pulmonary Critical Care & Sleep Disorders Medicine, Southlake Clinic, Valley Medical Center, Renton, WA

Dr. Wall reports no financial relationship to this field of study.

SYNOPSIS: In this modeling study of the possible effects of establishing a regional weaning facility in an area currently without such resources, whether cost savings would likely be achieved depended on numerous factors, including how much care at the weaning facility costs in relation to care in the ICU.

SOURCE: Lone NI, Walsh TS. Prolonged mechanical ventilation in critically ill patients: Epidemiology, outcomes and modelling the potential cost consequences of establishing a regional weaning unit. Crit Care 2011;15:R102.

Although most critically ill patients require only short periods of respiratory support, a minority require prolonged mechanical ventilation (PMV). When these patients linger in the intensive care unit (ICU), they create a challenge for acute care hospitals because they tie up beds and ventilators, reduce hospital throughput, and drive up health care costs. In some U.S. cities, these patients are ultimately transferred to long-term acute care (LTAC) facilities for ventilator weaning. In other cities, however, LTAC facilities are not available. In the United Kingdom (UK), LTAC facilities do not exist.

The authors of this study used a large comprehensive database from southeast Scotland to model whether a hypothetical ventilator weaning unit would be beneficial to the local community. The main objectives of this study were to: 1) establish the incidence of PMV in a large UK region; 2) examine the characteristics and outcomes of PMV patients; and 3) model the potential impact on costs and outcomes of establishing a regional ventilator weaning unit. PMV was defined as requiring mechanical ventilation (MV) ≥ 21 days. The authors performed a retrospective cohort study using a prospectively collected anonymous dataset from a community of 900,000 who are served by three adult hospitals. Each hospital has a "closed" adult general mixed medical/surgical ICU with intensivist staff. The hospitals are essentially managed as a single organization. The dataset captures every admission episode. It has been previously validated and has 94% accuracy.

The authors ran a variety of sensitivity analyses, a technique wherein they modeled various possible scenarios and inputs. For example, they ran their model using two different definitions of PMV. In the first definition, patients were mechanically ventilated for ≥ 21 consecutive days (with a required minimum of 6 hours daily). In the second definition, patients simply had to be ventilated for 21+ cumulative days during the hospitalization. When calculating incidence, the authors used different denominator definitions. The first denominator included every ICU admission irrespective of MV status. The second denominator only included ICU admissions requiring MV at some point during their stay.

The authors ran additional sensitivity analyses in which they varied aspects of the new hypothetical weaning unit. They varied the unit's admission criteria. Some units accepted patients on renal

Table. Characteristics and Outcomes of ICU Patients Requiring and Not Requiring Prolonged Mechanical Ventilation (PMV)

	PMV	Non-PMV	P value
Age, mean (years)	59.6	56.9	0.001
Female, %	42	43	0.86
APACHE II	21	18.8	< 0.001
Surgical, %	19	25	< 0.001
MV on day 1, %	92	66	< 0.001
PaO2/FiO2, median (mmHg)	139	227	< 0.001
Tracheostomy during admit, %	63	6	< 0.001
Hospital mortality, %	40	34	0.02
ICU mortality, %	26	23	0.23
ICU length of stay, median (days)	33	2	
Hospital length of stay after ICU discharge, median (days)	17	7	< 0.001

replacement therapy (RRT), others did not. Some units accepted patients within 48 hours after discontinuing pressors, others required 7 days of hemodynamic stability. This resulted in four different units, one which took patients on RRT 48 hours after weaning pressors (least stable), one that refused patients on RRT and didn't take patients until 7 days after pressors (most stable), and two units in between. They varied the cost of a weaning bed between 50% and 100% of an acute ICU bed. They estimated likely refusal rates depending on both bed availability and the admission criteria. They used these data to determine the optimal number of beds that made most financial sense for the community.

Overall, they examined 7848 admission episodes over a 5-year period. The incidence of PMV ranged between 4.4 and 6.3 per 100 ICU admissions. These patients utilized almost one-third of all ICU bed days. The most common diagnoses for all ICU patients were pneumonia, sepsis, and trauma. The diagnoses most associated with PMV were Guillain-Barré syndrome, pancreatitis, acute respiratory distress syndrome, pneumonia, and sepsis. In general, 8%-10% of ICU beds were occupied by PMV patients who could potentially be transferred. Other characteristics of PMV and non-PMV patients are listed in the table.

In the best-case scenario, establishing a regional weaning unit resulted in annual cost savings of approximately $600,000. In the worst-case scenario, the unit costs $56,000 annually. In addition, once a weaning unit bed reached 70% of the cost of an ICU bed, it was no longer cost saving. Of note, costs in the UK are not necessarily equivalent to the U.S. health care system.

■ COMMENTARY

While prospective randomized trials are excellent methods for rigorously testing discrete interventions, they are not well suited to real-world scenarios that typically involve multiple, interacting, and uncertain factors. Although observational studies using administrative data can generate hypotheses, they rarely can answer questions about the "next best step." In such cases, modeling the various hypothetical situations is often a much more practical approach.

In this study, PMV patients consumed a substantial amount of a region's health care resources. To address this issue, the authors modeled various scenarios to determine whether a community should build a weaning unit. I'm sure one could find faults with this study. For example, the authors did not account for the potential impact of the unit on patient outcomes, namely duration of MV or mortality. However, I think the authors nonetheless did a nice job. They used a preexisting database to minimize selection bias, and they performed numerous sensitivity analyses to address the uncertainty we all face in our practices. As providers and administrators are increasingly forced to make large sweeping decisions while also containing costs, I suspect we will begin to see more such studies. ■

ABSTRACT & COMMENTARY

Low Tidal Volume Ventilation in the Absence of Acute Lung Injury: A Study in Post-Cardiac Surgery Patients

By David J. Pierson, MD, Editor

SYNOPSIS: This randomized study of low-tidal-volume ventilation during and after cardiac surgery, in comparison to ventilation with tidal volumes of 10 mL/kg predicted body weight, showed no differences in median ventilation time but higher rates of extubation by 6 and 8 hours postoperatively and fewer reintubations in the low-tidal-volume group.

SOURCE: Sundar S, et al. Influence of low tidal volume ventilation on time to extubation in cardiac surgical patients. Anesthesiology 2011;114: 1102-1110.

Supported by robust data from numerous clinical trials, low-tidal-volume ventilation is now standard-of-care in managing patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS). While the tidal volumes used in ventilating non-ALI patients have generally decreased in the last two decades, no clinical studies have directly shown that deliberate low-tidal-volume ventilation to the extent applied in ALI is beneficial in that patient population. To address this issue, investigators at Beth Israel Deaconess Medical Center in Boston assessed time to extubation and several other factors in patients undergoing elective cardiac surgery who were randomized to be ventilated with tidal volumes of either 6 or 10 mL/kg predicted body weight.

Sundar and colleagues evaluated 621 patients who were to undergo cardiac surgery in their institution. They excluded emergent cases, patients on inotropic agents or intra-aortic balloon support, and those with pre-existing pulmonary disease or active infection, enrolling 74 patients in the low-tidal-volume arm and 75 in the control arm of the study. The allocated tidal volume was applied immediately following intubation, during surgery, and throughout the period of postoperative mechanical ventilation in the cardiothoracic ICU. Mechanical ventilation, sedation, and weaning and extubation were applied according to established protocols. The primary end point was time to extubation, with secondary analyses performed on other aspects of intubation time and the rate of reintubation.

Median total ventilation time was 7.5 hours vs 10.7 hours in the 6- and 10-mL/kg tidal volume groups, respectively (P = 0.10). At 6 hours from intubation, more patients in the 6-mL/kg group had been extubated (37%) than in the 10-mL/kg group (20%; P = 0.02). Corresponding proportions at 8 hours were 53% vs 31% (P = 0.0006). More patients in the larger-tidal-volume group required reintubation (9.5%) than in the low-tidal-volume group (1.3%; P = 0.03). There were no differences between the groups with respect to ICU or hospital lengths of stay.

COMMENTARY

Several studies have suggested that large-tidal-volume mechanical ventilation of critically ill patients without ALI predisposes them to development of that condition. Despite the facts that postoperative ventilation in cardiac surgery patients typically lasts only a few hours, and that this group of patients is generally at low risk for developing ALI or ARDS, there is evidence from studies of blood cytokines and other potential mediators of lung injury that the use of tidal volumes of 10-12 mL/kg predicted body weight may increase risk in this setting. This type of evidence, along with the finding that ALI and ARDS frequently go unrecognized by their physicians, supports arguments by some authorities that virtually all patients subjected to mechanical ventilation in the context of acute illness should be managed with low-tidal-volume, so-called lung-protective ventilation.[1]

This study was carried out in a single center, and excluded higher-risk cardiac surgery patients, limiting its generalizability even to the management of this restricted patient population of ventilated patients in other institutions. However, regardless of whether one accepts the authors' positive spin on their findings, the fact that no downside to low-tidal-volume ventilation

was demonstrated lends strength to the notion that this approach to ventilatory support is reasonable in patient populations well beyond those with ALI and ARDs. ■

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ABSTRACT & COMMENTARY

Patients/Surrogates Vastly Overrate Likelihood of Survival after Cardiac Arrest

By Leslie A. Hoffman, RN, PhD

Department of Acute/Tertiary Care, School of Nursing, University of Pittsburgh

SYNOPSIS: Most (83%) patients/surrogates stated they preferred full code status but only 4% could identify the components of CPR; 16% stated preferences that differed with the medical record.

SOURCE: Gehlbach TG, et al. Code status orders and goals of care in the medical ICU. Chest 2011;139:802-809.

Participants in this study were 100 patients/surrogates and their physicians in a 26-bed medical ICU located in an academic medical center. Patients/surrogates were questioned regarding their knowledge of cardiopulmonary resuscitation (CPR), code status preferences, and goals of care. Physicians were queried about goals of care and treatment plans. Interviews were conducted by a critical care fellow who selected participants from a randomized list of bed numbers generated each study day. The final sample included 20 patients and 80 surrogates. Fifty patients/surrogates recalled discussing CPR preferences with a physician, and 51 recalled discussing goals of care. Most (83%) stated they preferred full code status, but only 4% could identify the three main components of in-hospital CPR (defibrillation, chest compressions, intubation). Almost all charts (98%) documented code status. For 16%, discrepancies existed between patient/surrogate's stated preference during the interview and orders in the medical record. Patients/surrogates estimated survival to hospital discharge following in-hospital cardiac arrest with CPR at 71.8% (range, 10% to 100%) and the higher the prediction of survival, the greater the frequency of preference for full code status (P = 0.012). Of six possible goals of care, approximately five were affirmed by each patient/surrogate and physician, but 67.7% of patients/surrogates differed from their physicians about the most important goal of care.

■ COMMENTARY

When making decisions about code status orders, it is important to communicate effectively so that patients and families receive care that respects their preferences. Discussions about code status can be challenging and misunderstandings can lead to unwanted interventions. Findings of this study suggest that patients/surrogates rate their understanding as "high" but in reality do not fully understand what is involved in procedures commonly used in critical illness (e.g., CPR), and the likely outcome. Patient/surrogate estimates of survival after CPR in the ICU were extremely high (71.8%) compared to an evidence-based likelihood of 16% for ICU patients and 18% for patients on general wards. When queried about what was involved in CPR, most (65%) participants believed they had good knowledge of what CPR involved and most (71%) were able to identify use of chest compressions. However, far fewer identified cardiac defibrillation (32%) or the potential for intubation (7%). Study findings did not identify whether the problem related to clinicians not clearly describing possible outcomes or patients/surrogates indicating they understood when, in fact, they did not.

Discussions about decision making at the end-of-life are inherently challenging. Of note, the majority (80%) of participants in this survey felt it was helpful to talk about chances of survival after CPR and helpful (70%) to specifically discuss the goals of care. The take-home message from this study is that patients/surrogates may have an incomplete or incorrect understanding that is not recognized without probing questions. In this age of television dramas in which the "patient" almost always fully recovers, it is perhaps not unexpected that patients/surrogates have an incomplete understanding, as evidenced in this study. ■

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CME/CNE Questions

18. Risk factors for drowning include:

a. diabetes mellitus.
b. female sex.
c. tobacco use.
d. seizure disorders.
e. All of the above

19. Recommended interventions for victims of drowning include:

a. induced hypothermia.
b. heimlich maneuver.
c. hypertonic saline.
d. barbiturate coma.
e. drying and warming.

20. Which of the following is *true* about patients requiring prolonged mechanical ventilation (PMV)?

a. Less than 1% of ICU admits ultimately require PMV.
b. PMV patients tend to be older and sicker.
c. PMV patients are more likely to die in the ICU.
d. Trauma patients are the main group requiring PMV.
e. None of the above

21. Which of the following is *true* about the cost-effectiveness of a regional weaning unit for patients requiring PMV, according to the study from the United Kingdom?

a. The unit was cost-effective under all the modeling conditions evaluated.
b. The unit was net neutral under all the modeling conditions evaluated.
c. The unit failed to reduce the overall cost of care regardless of the model used.
d. Once the cost of a weaning unit bed exceeded 70% of that of an ICU bed, no cost saving occurred.
e. The economic situation in the study was essentially identical to that in the United States.

22. When patients/surrogates were questioned about code status and goals of care:

a. 40% recalled discussing CPR preferences with a physician.
b. the majority identified CPR as including possible intubation.
c. survival expectations exceeded expected based on evidence.
d. patients/surrogates preferred physicians to determine goals of care.

23. According to the evidence, which of the following is closest to the actual survival rate following CPR for cardiac arrest in ICU patients?

a. 2%
b. 8%
c. 16%
d. 32%
e. 64%

24. In the study of 6- vs 10-mL/kg tidal volumes for mechanical ventilation during and after elective cardiac surgery, patients who received the smaller volumes:

a. had shorter median duration of mechanical ventilation.
b. got out of the ICU faster.
c. had shorter hospital lengths of stay.
d. All of the above
e. None of the above

25. In the study of 6- vs 10-mL/kg tidal volumes for mechanical ventilation during and after elective cardiac surgery, patients who received the smaller volumes:

a. were more likely to be free of mechanical ventilation 6 hours after intubation.
b. were more likely to be free of mechanical ventilation 8 hours after intubation.
c. were less likely to require reintubation.
d. All of the above

CME/CNE Instructions

To earn credit for this activity, please follow these instructions:

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2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.
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CME/CNE Objectives

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

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In this issue: FDA issues multiple drug safety alerts; ARBs and cancer risk; and FDA actions.

Avoid high-dose simvastatin

The FDA is advising physicians to avoid high-dose simvastatin (Zocor) because of the risk of myopathy and rhabdomyolysis. The agency is advising that patients should not be started on the 80 mg dose and patients who already are on 80 mg should be continued only if they have been on that dose for 1 year or longer. The recommendations are based on results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocystine (SEARCH) trial — a 7-year randomized, controlled trial comparing the efficacy and safety of simvastatin 80 mg vs simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction. There was no significant difference in the incidence of major vascular events between the two doses; however, 52 patients (0.9%) in the 80-mg group developed myopathy vs one patient (0.02%) in the 20-mg group. Of the high-dose group, 22 patients (0.4%) developed rhabdomyolysis vs no patients in the 20-mg group. The risk for myopathy and rhabdomyolysis with simvastatin 80 mg was highest in the first 12 months of treatment. Of concern, the risk of myopathy was approximately doubled in patients taking a calcium channel blocker, particularly diltiazem. The majority of patients who developed myopathy also had a genetic variant that affects coding of the transporter responsible for simvastatin uptake in the liver, resulting in higher serum simvastatin levels. The FDA not only recommends against using simvastatin 80 mg, but also suggests that the drug is contraindicated for use in patients taking itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. The maximum dose of simvastatin should be only 10 mg in patients taking amiodarone, verapamil, and diltiazem while the maximum dose is 20 mg in patients taking amlodipine and ranolazine. The new guidance recommends using a different statin if the patient's LDL targets aren't met with the 40-mg simvastatin dose. The loss of high-dose simvastatin comes as a blow to cost-concious consumers who now likely will be prescribed brand name atorvastatin (Lipitor) or rosuvastatin (Crestor). Generic atorvastatin is likely to be available in late 2011. ■

Increased risk of prostate cancer

The FDA has issued a somewhat controversial warning regarding an increased risk for high-grade prostate cancer associated with the 5-alfa reductase inhibitors finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn). Ironically, the new warning stems from studies designed to evaluate whether the drugs offer protection *against* prostate cancer. Both drugs are marketed to treat benign prostate hypertrophy and both are known to significantly decrease the prostate-specific antigen levels. In separate studies, both drugs were investigated to see if they reduce the incidence of prostate cancer. FDA experts reviewed the results of the Prostate Cancer Prevention Trial (PCPT), which evalu-

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ated finasteride vs placebo for 7 years, and the Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE), which compared dutasteride to placebo for 4 years. Prostate cancers were significantly reduced in both trials; however, the reduction was limited to low-grade prostate cancers with a Gleason score of 6 or lower. The rate of cancers with a Gleason score of 8-10 was increased in both studies. Previous analyses of these data have suggested that finasteride did not increase the risk of high-grade prostate cancers, but rather made them easier to diagnose by decreasing the volume of the prostate (*Clin Cancer Res* 2009;15:4694-4699; *J Natl Cancer Inst* 2007;99:1366-1374). The FDA panel, however, disagrees and feels it prudent to add a warning to labeling of both medications regarding increased risk of high-grade prostate cancer associated with use of the drugs. The guidance further recommends that prior to initiating therapy patients should be evaluated to rule out other urologic conditions, including prostate cancer, that might mimic benign prostatic hypertrophy. ■

Actos and bladder cancer risk

The diabetes drug pioglitazone (Actos) is the subject of a new warning from the FDA regarding possible bladder cancer risk associated with use of the drug. The FDA ongoing safety review suggests that use of pioglitazone for more than 1 year may be associated with increased risk of bladder cancer based on review of a 5-year interim analysis of an ongoing 10-year epidemiologic study. Patients who had been on pioglitazone the longest and who had the highest cumulative dose of the drug had a slightly increased risk of bladder cancer. This warning falls on the heels of a French study that also showed increased risk of bladder cancer. Based on these findings, France's drug regulatory agency has suspended use of the drug. While the FDA is not recommending withdrawing the drug from the market, it does recommend avoiding pioglitazone in patients with active bladder cancer and using it with caution in patients with prior history of bladder cancer. Thiazolidinediones — including pioglitazone — have also come under scrutiny in recent years because of increased risk of congestive heart failure and bone fractures in females. ■

Chantix and cardiovascular events

The FDA has issued an alert regarding varenicline (Chantix) regarding a small increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. The warning regarding the smoking cessation drug was the result of review of a randomized, double-blind, placebo-controlled trial of 700 smokers with cardiovascular disease who were treated with varenicline or placebo. The overall rate of adverse effects was low but cardiovascular events, including heart attack, were reported more frequently in the treatment group. The warning will result in a change in labeling for the drug and the FDA is also requiring Pfizer, the drug manufacturer, to conduct an analysis of other trials to further assess the risk. Varenicline already carries a box warning regarding neuropsychiatric symptoms including suicidality. ■

ARBs and cancer risk

Finally some good news from the FDA. After a 2010 meta-analysis showed a possible link between angiotensin receptor blockers (ARBs) and cancer, the agency has completed its own review and has found no evidence of increased risk of "cancer events" including new cancers, cancer-related deaths, breast cancer, lung cancer, or prostate cancer associated with the drugs. The agency conducted a much larger meta-analysis than the original study, including more than 150,000 patients in 31 long-term, randomized, controlled clinical trials. The rate of cancer events in the ARB group was 1.82 per 100 patient years while the rate in the non-ARB group was 1.84 per 100 patient years (relative risk of incident cancer in patients taking ARBs 0.99, 95% confidence interval, 0.92 to 1.06) There was no statistically significant difference in cancer death rates or incidence of individual cancer types. The agency continues to monitor this issue but currently states that the benefits of ARBs continue to outweigh the potential risks (summary available at FDA.gov/drugs/drugsafety/). ■

FDA actions

The FDA has approved the first generic version of levofloxacin (Levaquin). The popular fluoroquinolone is commonly used for treatment of respiratory infections, sinusitis, prostatitis, pyelonephritis and skin infections. Generic forms will include tablets, oral solutions, and injectable solutions.

The FDA has approved an abuse-resistant short-acting oxycodone tablet. Pfizer Pharmaceuticals has licensed the "AVERSION Technology" from Acura Pharmaceuticals. The technology prevents dissolving and injecting tablets by creating a gel when mixed with water or other solvents that prevents snorting crushed tablets by burning nasal passages, and also prevents intentional swallowing of excess quantities by adding niacin which causes intense flushing, itching, and sweating. Long-acting oxycodone (OxyContin) was similarly reformulated in 2010 to prevent misuse and abuse. ■