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Critical Care [ALERT]

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

ABSTRACT & COMMENTARY

TPN? And When?

By Saadia R. Akhtar, MD, MSc
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Dr. Akhtar reports no financial relationships relevant to this field of study.

SYNOPSIS: This randomized multicenter trial of the timing of initiation of parenteral nutrition for supplementation of enteral nutrition for ICU patients finds improved outcomes and fewer complications with late initiation.

SOURCE: Casaer MP, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011;365:506-517.

Casaer et al set out to determine the effects of late (day 8) vs early (within 48 hours) initiation of parenteral nutrition (TPN) on death rate and complications in adult intensive care unit (ICU) patients. The primary endpoint was number of days in the ICU.

This was a prospective, randomized, controlled, multicenter trial that took place between 2007 and 2010 at seven ICUs in Belgium. Inclusion criteria were evidence of nutritional impairment or significant risk for it (measured using a validated and standardized nutritional risk screen questionnaire) and age > 18 years. Exclusion criteria included being severely underweight (defined by body mass index), already being on nutritional supplementation, recent admission to the ICU, diabetic coma or moribund state, and absence of central venous catheter. Caloric targets were calculated for each patient. All patients began enteral nutrition by day 2 if unable to eat; semi-recumbent position was maintained. For the early-initiation group, a 20% glucose solution (D20) was administered intravenously for the first 2 days and then full TPN was started on day 3. For the late-initiation group, 5% glucose (D5) was given intravenously; if enteral nutrition was felt to be inadequate by day 8, TPN was added. Aggressive blood glucose control (80-110 mg/dL) was maintained with continuous infusion of intravenous insulin. TPN was stopped once at least 80% of calorie goal was met with enteral nutrition (or once the patient started to eat). Usual

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demographic, clinical, and outcome data were collected along with 90-day vital status. The authors applied appropriate randomization schemes, interim analysis, and statistical methods.

A total of 4640 patients were enrolled and randomized. Subjects were well-matched in terms of baseline characteristics. The late-initiation group had lower insulin needs and more hypoglycemic episodes. Despite this, ICU median length of stay (LOS) was 1 day shorter; risk of acquiring new infections was less; and duration of mechanical ventilation, renal replacement, and hospitalization were shorter in this group; there was also a mean cost reduction of about $1600 per patient. Functional status at hospital discharge and mortality at ICU and hospital discharge and 90 days were similar in the two groups.

COMMENTARY

An essential component of supportive care for any critical illness is nutrition, which serves to meet patients' metabolic needs and facilitate recovery. Although limited data demonstrate some benefits of enteral compared to parenteral nutrition (e.g., reduced infections, lower cost), both methods may have complications. Patients receiving enteral nutrition may develop aspiration (with subsequent pneumonia), diarrhea, or constipation. Administration of TPN may lead to thromboses or bloodstream infections related to the central venous access. Hyperglycemia and other metabolic abnormalities and fluid imbalance can be a concern with either method of nutritional support. In general, recent practice has been to favor enteral nutrition with aspiration precautions and careful blood glucose control; however, it has been unclear whether or when to add TPN if caloric targets cannot be met with enteric feeding alone.

This study provides some useful information, showing that early initiation of TPN in ICU patients is associated with worse outcomes. It is important though to note that although the relative benefits of late initiation of TPN in this study were significant, they were small; for example, a 1-day difference in ICU LOS and 3.4% difference in new infections, without an impact on mortality. Furthermore, the majority of patients studied were being admitted for elective cardiac surgery and had good baseline nutritional status. It is difficult to know whether these results apply consistently to sicker, malnourished ICU patients.

I suggest initiating enteral nutrition within the first 2-3 days of a patient's admission to the ICU whenever possible. If goal caloric intake cannot be achieved rapidly, it is prudent to wait and tolerate some degree of underfeeding for the first week. The exception to this may be the patients who have very significant malnutrition at baseline; here, our individual clinical judgments about initiation of TPN must prevail until further clinical trials are completed. ■

ABSTRACT & COMMENTARY

Saddle Pulmonary Embolism: Is It the Same as 'Massive' PE?

By David J. Pierson, MD, Editor

SYNOPSIS: Saddle pulmonary embolism was found in 37 of 680 patients with documented pulmonary embolism (PE) in this community hospital study. The great majority of these patients did well on standard therapy without thrombolytics, emphasizing that the radiographic finding of saddle PE should not by itself be equated with the much more serious clinical entity of massive PE.

SOURCE: Sardi A, et al. Saddle pulmonary embolism: Is it as bad as it looks? A community hospital experience. *Crit Care Med* 2011;Jun 23. [Epub ahead of print]

Saddle pulmonary embolism (SPE) is defined as the presence of a thromboembolus located at the bifurcation of the main pulmonary artery. Once identified at post-mortem examination or by pulmonary arteriography, SPE is now most commonly encountered by clinicians as a radiographic finding on computed tomography angiography (CTA). The authors of this retrospective study of all CTAs that were read as positive for PE over a 4.75-year period at Albert Einstein Medical Center in Philadelphia sought to determine the clinical features, associated findings, management, and outcomes of all patients with SPE. Patients older than 18 years were identified by IDC-9 codes indicating a positive CTA for PE, and the images were then reviewed independently by two radiologists who were unaware of the patients' clinical status or other data. The findings on transthoracic echocardiography (TTE) on patients determined to have SPE by CTA were assessed by standardized criteria, and other clinical information was extracted from the patients' charts.

During the study period, which ended in early 2009, 680 patients had the diagnosis of PE established by CTA, and 37 (5.4%) of them met the authors' criteria for SPE. With a median age of 60 years, these patients were predominately women (60%) and African American (84%), and 81% of them were admitted through the emergency department. The most frequent comorbidities were history of stroke (24%), surgery within 3 months (24%), and malignancy (22%). Fifteen of the 37 patients (41%) were admitted to the ICU and one required mechanical ventilation.

The amount of thrombus present by CTA in the patients with SPE, estimated using a 40-point clot burden score, was a median of 31 points, believed to correspond to 79% occlusion. The median radiographic right-to-left ventricle diameter ratio was 1.39 (normal < 0.7), with a median pulmonary artery-to-aorta diameter ratio of 1.0 and a median superior vena cava diameter 23 mm. TTE was performed in 27 of the 37 patients with SPE (73%); 21 (78%) had right ventricular enlargement, which was severe in seven patients, moderate in eight, and mild in six. Right ventricular dysfunction by TTE was noted in 21 patients (78% — severe in five, moderate in eight, and mild in seven), and 18 (67%) had elevated pulmonary arterial systolic pressure (not defined). Interventricular septum flattening and/or leftward deviation was found in seven patients (26%).

Transient hypotension occurred in six patients (16%) and persistent shock (systolic blood pressure 90 mmHg or less after intravenous administration of at least 500 mL of crystalloid) was present in three (8%). Most of the patients (87%) were treated with unfractionated heparin, and only four (11%) received thrombolytics. One heparin-treated patient had a gastrointestinal bleed; two who were given thrombolytics had major and a third had a minor hemorrhagic complication. Seventeen patients (46%) received inferior vena cava filters. Two patients died, one in the emergency department, presumably of PE, and one 2 weeks after admission with multiple-organ failure.

COMMENTARY

This study's authors asked the following research question: "What are the demographics, laboratory findings, TTE results, CTA findings, treatment, and outcomes of patients with SPE in our institution?" This is the type of question that can be addressed pretty well in a retrospective study, as long as relevant data are available on a high proportion of all patients with the variable of interest (SPE in this case). A more important (though unstated) research question would be, "What are the clinical implications of the radiographic finding of SPE among patients with CTA-confirmed PE?" Unfortunately, the present study cannot help us with this second question, which would require comparing the information in the paper with the same data from an appropriately-selected control group — in this instance, a sample of the 94.6% of all patients with PE who did not have SPE. As it is, while the description of this consecutive case series adds to the literature on SPE, the applicability of the findings beyond the authors' institution is uncertain, and the most important questions about what the clinician should do when the radiologist reports the finding of SPE remain unanswered.

One thing this study brings out, though, is the distinction between SPE and massive pulmonary embolism (MPE). MPE is a clinical syndrome with high mortality defined by the degree of hemodynamic compromise present in a patient with acute PE — essentially, cardiogenic shock or persistent hypotension, further specified as a systolic blood pressure persistently < 90 mmHg, or a drop in baseline blood pressure of at least 40 mmHg for > 15 minutes.[1] SPE is very common among patients with MPE, but the reverse is not necessarily the case, as the data of Sardi et al illustrate. CTA has become the gold standard for diagnosing PE, and is performed far more often today than in past decades. Today, clinicians are increasingly likely to hear the words "massive pulmonary embolism" from a radiologist,

meaning that the clot burden visualized on the exam is extensive, and it is important to realize that this term can be used in more than one way. Additional studies are needed to determine whether the finding of SPE by itself constitutes an important prognostic factor, or whether it should be taken into consideration separately from other clinical information in deciding how the patient with acute PE should be managed. ■

REFERENCE

1. Kucher N, Goldhaber SZ. Management of massive pulmonary embolism. *Circulation* 2005;112:e28-32.

ABSTRACT & COMMENTARY

Risks of ICU Admission Include Unintentional Discontinuation of Medications

By Leslie A. Hoffman, RN, PhD

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

SYNOPSIS: Admission to an ICU increased risk for unintentional medication discontinuation in four of five medication groups commonly used to manage a chronic illness.

SOURCE: Bell CM, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. *JAMA* 2011;306:840-847.

To determine the risk of potentially unintended discontinuation of common, evidence-based medications for chronic disease, Bell and colleagues examined administrative records for 12 years (1997–2009) for all hospitalized patients and all outpatient prescriptions in Ontario, Canada. Patients were included if they were ≥ 66 years of age and continuously prescribed one of five medications for at least 12 months: 1) statins, 2) antiplatelet/anticoagulants, 3) levothyroxine, 4) an inhaled respiratory drug (anticholinergic, beta-agonist, steroid), or 5) a gastric acid-suppressing drug. Three cohorts were formed: 1) patients discharged after an admission that included an ICU stay (n = 16,474), 2) patients discharged after an admission that did not include an ICU admission (n = 171,438), and 3) patients not hospitalized (controls; n = 208,468). The study controlled for a number of potential confounding variables, including age, sex, income, length of stay, and disease burden (number of medications prescribed). Separate analyses were performed for each of the five medication groups.

Patients admitted to a hospital were more likely to experience a potentially unintentional discontinuation of a medication compared to controls across all medication groups examined. The adjusted odds ratio (AOR) ranged from 1.18 (95% confidence interval [CI], 1.14-1.23) for discontinuing levothyroxine in 12.3% of hospitalized patients vs 11.0% of controls to an AOR of 1.86 (95% CI, 1.77-1.97) for discontinuing antiplatelet/anticoagulant agents in 19.4% of hospitalized patients vs 11.8% of controls. With ICU exposure, the AOR ranged from 1.48 (95% CI, 1.39-1.57) for discontinuing statins in 14.6% of ICU patients to an AOR of 2.31 (95% CI, 2.07-2.57) for discontinuing antiplatelet/anticoagulant agents in 22.8% of ICU patients vs the control group. Admission to an ICU was associated with an additional risk of medication discontinuation in four of five medication groups compared to hospitalizations without an ICU admission. A 1-year follow-up of patients with discontinued medications showed an elevated AOR for the secondary composite outcome of death, emergency department visit, or emergent hospitalization of 1.07 (95% CI, 1.03-1.11) for statins and of 1.10 (95% CI, 1.03-1.16) in the antiplatelet/anticoagulant agents group.

■ COMMENTARY

This study highlights a serious risk factor common to all care transitions. When patients change care providers, critical information may be omitted or not clearly communicated, resulting in an increased risk for adverse events. In this study, hospitalized patients experienced an increased risk for unintentional discontinuation of a medication at discharge. Admission to an ICU was associated with a higher risk for this outcome. At 1 year, there

was an increased risk of death, an emergency department visit, or emergent hospitalization when two groups of medications — statins and antiplatelet/anticoagulant agents — were not continued after hospitalization.

Given the retrospective design, it is possible that decisions to discontinue medications may have been intentional. However, the authors took multiple steps to minimize this potential. All of the selected medications had well-established long-term efficacy for the management of a chronic disease. Only patients who had taken the medication continuously for 1 year were included. Unintentional discontinuation was defined as no renewal within 90 days plus a grace period to allow for medications remaining from past prescriptions. New prescriptions within the same drug classification were not categorized as a discontinuation. Given these constraints, the percentage of patients who experienced unintentional medication discontinuation is very alarming. For hospitalized patients, antiplatelets/anticoagulants (19.1%) led, followed by statins (13.5%), gastric acid suppressors (12.7%), levothyroxine (12.1%), and respiratory inhalers (4.4%). For ICU patients, the sequence was the same but the percentage was higher, e.g., antiplatelets/anticoagulants (22.8%), followed by statins (14.6), gastric acid suppressors (15.4%), levothyroxine (15%), and respiratory inhalers (5.4%). The authors posed several explanations for a higher risk in ICU patients. ICU patients likely experience more transitions. Care is focused on the critical episode, not an underlying chronic illness. Some medications get discontinued and this increases the risk that they will be forgotten at ICU discharge.

Given these findings, what can be done to improve patient safety? Enhanced awareness of the potential for unintentional discontinuation on the part of all providers is one option. However, the hectic nature of critical care makes it doubtful that omissions will not occur, despite good intentions. The best solution is likely electronic medical records that list prior medications and, therefore, make it easier to recall what needs to be continued or reordered during each care transition. ■

ABSTRACT & COMMENTARY

Daily Prompting on ICU Checklist Use Improves Patient Outcomes as Well as Processes of Care

By David J. Pierson, MD, Editor

SYNOPSIS: In this study from a single medical ICU, prompting physicians to discuss all six items on a daily rounding checklist, as compared with the use of the same checklist without prompting, significantly improved several processes of care and appeared to decrease length of stay and mortality as well.

SOURCE: Weiss CH, et al. Prompting physicians to address a daily checklist and process of care and clinical outcomes: A single-site study. *Am J Respir Crit Care Med* 2011;184:680-686.

Previous studies have shown that the use of a multi-part daily rounding checklist reduces errors of omission in the ICU — such as failure to discontinue empirically started antibiotics, to perform spontaneous breathing trials to see whether ventilated patients can be weaned and extubated, or to provide prophylaxis against deep venous thrombosis (DVT). This study sought to determine whether daily prompting of physicians to deal with the items in such a checklist during ICU rounds would improve processes of care and patient outcomes in comparison to simply introducing the same checklist into the ICU.

The study was carried out in the medical ICU of a major academic medical center. After introduction of the ICU rounding checklist to the unit, patients cared for by the two unit teams (each with an attending physician, ICU fellow, several residents, and a clinical pharmacist) comprised a control group and an intervention group. In the intervention group, a resident working on the study came on rounds (but had no involvement with managing the patients) and prompted the attending or fellow

to discuss any of the six target items omitted from the checklist while the team was still rounding on each patient. The control team had the checklist available but no explicit efforts were directed at its implementation on rounds. Data from 1283 patients admitted to the unit before the checklist was introduced were compared to prospective data collected from intervention and control patients during the 82-day study period.

The checklist contained color-coded items to be filled out by nurses (e.g., lines and tubes), pharmacists (e.g., antibiotics and DVT prophylaxis), and physicians (e.g., sedative use and appropriateness of daily weaning trial), and entries were to be made each day the patient remained in the ICU. There were 140 patients in the intervention (prompted) group and 125 in the control group. Patient demographics, admitting diagnoses, time and day of admission, illness severity (APACHE IV), and proportion requiring mechanical ventilation (29%) were the same in the two groups.

The prompter was present on 68% of study days in the intervention group, although all days and patients in that group were included. Overall, prompting on at least one omitted checklist item occurred on 65% of patient days — i.e., the great majority of days on which the prompter attended rounds. Of the six items targeted for prompting, discussion of continued need for a Foley catheter was most frequently omitted (41% of patient days), followed by empirical antibiotics (36%), a central venous catheter (26%), mechanical ventilation (14%), DVT prophylaxis (1.5%), and stress ulcer prophylaxis (1%).

Compared with the control group, the prompted group had more median ventilator-free days (22 vs 16, $P = 0.028$), fewer days of empirical antibiotics (2 vs 3, $P = 0.012$), shorter duration of central venous catheter (3 vs 5 days, $P = 0.007$), and significantly more administration of DVT and stress-ulcer prophylaxis. Although hospital mortality was not different between the retrospectively examined preintervention patients and the control group, both ICU and hospital mortalities were lower in the prompted group (9% vs 17%, $P = 0.05$). APACHE IV-predicted ICU lengths of stay were the same in the control and prompted groups, but prompted patients had shorter ICU stays when calculated according to observed/predicted length of stay ratio (0.59 vs 0.87, $P = 0.02$). The authors conclude that daily prompting on checklist use improved multiple processes of care and may also have reduced mortality and length of stay, compared with the presence of the checklist without such prompting.

■ COMMENTARY

In this study, preintervention process-of-care data from the same unit (no checklist) were not different from results in the control group after the checklist was added. Little information is provided about just how the checklist was introduced in the unit. However, studies showing improved outcomes with checklists have also implemented substantial cultural change in the institution at the same time. In this study the cultural change was the prompting, and the control group results suggest that simply having a checklist available in the unit is not sufficient to change practice.

Patients managed by the team in which daily physician prompting occurred had improved processes of care and better outcomes. But several questions are raised as to how this finding might persist with different prompting scenarios. The prompter here was a physician (a resident), obviously an unrealistic situation for broader implementation. Would attending physicians and fellows (or community practitioners) be as receptive to real-time, face-to-face prompting by a nurse, or a clinical pharmacist — or a non-clinical hospital employee — during ICU rounds? Would some sort of automated, computerized prompting, perhaps tied to electronic order entry, work as well?

As pointed out by the authors, small pilot studies from single sites may have more impressive results than larger-scale multicenter studies of the same intervention. However, if the findings of this study hold up in broader contexts and with larger investigations, just how prompting is to be done may become an important issue. The decreased antibiotic use, shorter duration of mechanical ventilation, and reduced ICU length of stay found in this study have substantial potential economic implications that might be of interest to system administrators, third-party payers, and regulators. Some form of checklist-based, real-time prompting might well become part of daily practice in the ICU, making this matter one of considerable interest to the clinicians who work there. ■

CME/CNE Questions

1. The study of early vs late parenteral nutrition:

a. focused on underweight ICU patients.

b. defined early as within the first week of ICU admission.

c. included patients eating orally.

d. did not specify glucose targets/control.

e. None of the above

2. Late parenteral nutrition (TPN) compared to early initiation of TPN resulted in:

a. shorter stays in the ICU.

b. reduced 90-day mortality.

c. increased risk of infection.

d. lower albumin levels.

e. All of the above

3. In the retrospective series of patients with saddle pulmonary embolism, which of the following is closest to the proportion of those with this finding who died during the hospitalization?

a. 5%

b. 10%

c. 15%

d. 25%

e. 45%

4. Which of the following is the most correct definition of massive pulmonary embolism?

a. Demonstration of saddle pulmonary embolism by computed tomography

b. A clot burden index of > 30 (out of a possible 40)

c. Systolic blood pressure < 90 mmHg (or > 40 mmHg below baseline) for > 15 minutes

d. All of the above

e. None of the above

5. In ICU patients, unintentional discontinuation of a medication was least likely to occur when the patient was prescribed:

a. antiplatelets/anticoagulants.

b. statins.

c. gastric acid suppressors.

d. levothyroxine.

e. a respiratory inhaled drug.

6. At 1-year follow-up, patients whose medications were discontinued unintentionally experienced:

a. more deaths, emergency department visits, and emergency hospitalizations.

b. more deaths if diagnosed with atrial fibrillation or gastric reflux disease.

c. more deaths if diagnosed with COPD or heart failure.

d. fewer side effects due to polypharmacy.

e. no adverse effects.

7. In the study of daily prompting about the items on a rounding checklist, the person prompting the attending physician or fellow on omitted items was:

a. a pharmacist.

b. a nurse.

c. a respiratory therapist.

d. a non-clinical prompter from the insurance company.

e. another physician.

8. Daily prompting of physicians to discuss the six items on an ICU rounding checklist improved processes of care and patient outcomes in what clinical setting?

a. All the ICUs in an academic medical center

b. The ICUs in both an academic hospital and a community hospital

c. A mixed medical-surgical ICU in a community hospital

d. A medical ICU in an academic medical center

e. None of the above

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Medication Poisonings Are Increasing in Children

In this issue: Medication poisonings in children; rosuvastatin vs atorvastatin for atherosclerosis; saw palmetto for prostate symptoms; using atypical antipsychotics for off-label indications in adults; and FDA actions.

More medications, more poisonings

Medication poisonings among young children have increased in frequency in recent years despite safety measures to prevent them, according to a new study from *Pediatrics*. Researchers used patient records of more than 450,000 children 5 years old or younger from 2001-2008. The rate of poisoning increased by about a third during this time span compared to the prior decade. Child self-exposure was responsible 95% of the time with ingestion of prescription drugs causing more than half of the poisonings and more than 70% of significant injuries. The most dangerous drugs were opioids, sedative-hypnotics, and cardiovascular agents. The authors conclude that the number of children visiting emergency departments after medication exposure is increasing, with the majority of ingestions caused by children finding and ingesting medications by themselves. They suggest that efforts at poison-proofing homes with young children "may be a good, but insufficient, strategy." They further suggest that the increase in poisonings is in part due to the rise in number of medications in the environments of young children, with the number of adults taking medications, especially opioid medications, rising dramatically in the last 10 years. Other possible explanations include more siblings on medications, especially ADHD meds, as well as exposure to grandparents' homes where child-proofing may not be as rigorous. They further conclude that current preventive efforts are inadequate and new measures, such as efforts targeting home medication safety (including storage of medications and child-resistant closures) and repackaging (such as blister packs and flow restrictors on liquid medications), should be considered. (*Pediatrics* published online September 16, 2011.) ■

Rosuvastatin no better than atorvastatin

Rosuvastatin is no better than atorvastatin in slowing progression of coronary atheroma, according to AstraZeneca, the manufacturer of rosuvastatin and sponsor of the study. Researchers compared rosuvastatin 40 mg to atorvastatin 80 mg in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs Atorvastatin (SATURN) trial. The primary efficacy endpoint was change from baseline in percent atheroma volume in a targeted coronary artery as assessed by intravascular ultrasound. After 104 weeks of treatment in some 1300 patients, there was a numerical greater reduction in favor of rosuvastatin, but the reduction did not reach statistical significance (astrazeneca.com/Media/Press-releases). The full results will be presented at the American Heart Association meeting in

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November. The results come as a blow to the manufacturer of rosuvastatin (Crestor) who had hoped to gain a marketing advantage before the introduction of low-cost generic atorvastatin into the market, slated for December. ■

Saw palmetto for prostate symptoms

Saw palmetto is ineffective for treating lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH), even at higher doses, according to a new study. Previous studies have shown no benefit from saw palmetto, but researchers in this current study set out to test the efficacy of 2-3 times the normal daily dose on men over the age of 45 with significant LUTS. The main outcome was the difference in American Urologic Association Symptom Index score between baseline and week 72. Both saw palmetto and placebo led to an improvement in symptoms with a favorability toward placebo regardless of the dose of saw palmetto. Doses tested were a single 320 mg tablet per day with dose escalation to 2, then 3, tablets per day. The authors conclude that increasing doses of saw palmetto root extract did not lower LUTS more than placebo in men with BPH (*JAMA* 2011;306:1344-1351). This is the second rigorously controlled trial after the Saw Palmetto Treatment for Enlarged Prostates study (*N Engl J Med* 2006;354:557-566) to show no benefit from the supplement on LUTS in men with BPH. ■

Off-label use of atypical antipsychotics

Controversy surrounds the use of atypical antipsychotics for off-label indications in adults, especially the elderly with dementia. A new meta-analysis reviews the evidence of efficacy of these drugs for various off-label uses. Of more than 12,000 studies considered, 162 were included in the analysis. Drugs reviewed included risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), asenapine (Saphris), iloperidone (Fanapt), and paliperidone (Invega). For elderly patients with dementia, a small but statistically significant improvement in symptoms such as psychosis, mood alterations, and aggression were seen with aripiprazole, olanzapine, and risperidone. For generalized anxiety disorder, quetiapine was the most effective, while for obsessive-compulsive disorder, risperidone was associated with a 3.9 greater likelihood of favorable response, compared with placebo when used with antidepressants. There was no benefit seen with any of the drugs used in treating eating disorders, substance abuse, or insomnia, and only marginal benefit in personality disorders or posttraumatic stress disorder. All of these drugs have a boxed warning regarding increased mortality in elderly patients with dementia and increased risk of suicidality. Increased risk of death was seen in elderly patients with a number needed to harm (NNH) of 87. Also noted was increased risk of stroke, especially with risperidone (NNH = 53), extraparametal symptoms (NNH = 10 for olanzepine, NNH = 20 for risperidone), and urinary tract symptoms (NNH range = 16-36). Weight gain was also a problem in non-elderly adults, particularly with olanzapine (incidence of more than 40%), while akathisia was more common with aripiprazole. Other common side effects included fatigue, sedation, and extrapyramidal symptoms. (*JAMA* 2011;306:1359-1369). ■

FDA actions

The FDA has issued a warning regarding the potential for arrhythmia associated with the antinausea drug ondansetron (Zofran). The drug should be avoided in patients with QT prolongation as they are at particular risk of developing torsade de pointes. Ondansetron should be used with caution in patients with congestive heart failure, bradyarrhythmias, those predisposed to low potassium or magnesium, and in those taking drugs that cause QT prolongation. These patients should have electrocardiogram monitoring if ondansetron is indicated. The FDA is requiring new labeling changes to reflect these warnings.

The FDA is reminding physicians and patients that epinephrine inhaler (Primatene Mist), the only over-the-counter inhaler for asthma, will be removed from the market on December 31. The withdrawal is due to an international ban on chlorofluorocarbon propellant. The FDA is recommending that physicians ask their patients with asthma if they use Primatene Mist and talk to them about prescription alternatives.

The FDA has approved infliximab (Remicade) to treat moderate-to-severe ulcerative colitis (UC) in children 6 years and older who have had inadequate response to conventional therapy. The drug is already approved for adults with UC. The approval was based on a randomized, open-label trial of 60 children ages 6 to 17 with moderate-to-severe UC. The drug carries a boxed warning for serious infections and cancer. Infliximab is manufactured by Janssen Biotech. ■