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Critical Care [ALERT]

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

SPECIAL FEATURE

Successful Implementation of an Early Mobility Protocol in Critical Care

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Dr. McFeely reports no financial relationships relevant to this field of study.

Things done well and with a care, exempt themselves from fear.

— Henry VIII, Act 1, Scene 2

Patients who survive admission to the ICU often are left with long-term disabilities resulting both from their presenting illness and from the care they receive while there. For example, patients with acute respiratory distress syndrome (ARDS) have persistent exercise limitations and a reduced physical quality of life 5 years after their critical illness, despite having near normal pulmonary function.[1] Up to 50% of patients with prolonged ventilation, sepsis, or multiple organ systems failure develop neuromuscular dysfunction.[2] This weakness is independently associated with hospital mortality.[3] Severe sepsis in older patients is independently associated with substantial and persistent new cognitive impairment and functional disability among survivors.[4] The ICU cultural preference for immobility, coupled with excessive use of sedation, is leaving patients with long-term disabilities.

Successful implementation of an early mobility protocol, with its associated improvement in sedation and delirium management practices, can improve these outcomes. In a retrospective study of 280 patients with respiratory failure, lack of early mobilization was independently associated with higher rates of readmission and death.[5] In one well-executed, randomized trial of 100 mechanically ventilated patients, those who received early mobilization — physical therapy (PT) started on average 1.4 days after intubation vs 7.4 days — had fewer days of delirium and fewer

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Critical Care [ALERT]

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days on mechanical ventilation.[6] At the time of hospital discharge, 59% of the early mobility group were back to independent function as opposed to 35% of the control group.[6]

Successful implementation of a mobility protocol requires a cultural shift in ICU care.[7] Mobility has to be considered as important a therapeutic modality as ventilation bundles, nutritional support, skin care, and all the other outcome variables with which we now concern ourselves. Early mobility needs to be the rule rather than the exception. This cultural shift will be difficult. The preference of many senior staff for immobility and sedation, based on reasons of "safety," needs to evolve to a preference for mobility and alertness. We need to educate staff to understand that it is unsafe to oversedate patients, and that immobility harms them and leaves long-lasting disability.

Such cultural change requires a team of believers. ICU mobility is a multidisciplinary process and needs a champion from each involved discipline. At a minimum a physician, nurse, PT, and respiratory therapist (RT) champion are needed. These individuals will hopefully have enough gravitas to influence the behavior of others. In addition, some low-tech hardware — including a platform walker, seat cushions, eye shades, and ear plugs to facilitate sleep — is needed. Initially, the incremental additional PT and RT time can be absorbed by existing staff; but an early mobility protocol may require an additional full-time PT, especially if successful in a large unit. The goal should be to have 60-80% of ICU patients receiving PT daily.

There are patients for whom mobility is contraindicated (*see Table 1*). For all others, early mobility should be the default. The early mobility process goes through stages (*see Table 2*). Other than the PT time, no additional resources are needed until the point of sitting at the edge of the bed.

Table 1. Contraindications to Early Mobility

- Significant vasopressor requirement
- FIO_2 > 0.8; PEEP > 12 cm H_2O; worsening respiratory failure
- Use of paralytics
- Acute neurologic event (reassess daily)
- Unstable spine or extremities
- Comfort care status
- Femoral dialysis catheter
- Open abdominal wounds
- Unresponsiveness (reassess sedation orders)

Table 2. Stages of Mobilization

- Detangle all lines and tubes
- Range of motion in bed
- Sitting at the edge of the bed
- Assisted sit to stand (more RT time needed from here)
- Walking in place
- Walking in unit

The major barrier to early mobility is excess sedation.[8] Commonly, patients are sedated excessively at night, and then are unable to participate in activities during the day. To avoid this, an ICU committed to early mobility will make use of daily sedation vacations, lightened goals of sedation, and real-time feedback to staff when patients are unable to participate due to sedation. Facilitating sleep through environmental modifications, medication optimization, and minimization of patient care interruptions can help avoid delirium. Treating delirium with appropriate medications, rather than silencing delirium through sedation, will also help.

Other barriers to successful implementation exist (*see Table 3*). These barriers can be overcome in a variety of ways. The default activity level for ICU patients must become "as tolerated" rather than bed rest. Sedation goals need to default to alert, with Richmond Agitation Sedation Scale (RASS) = 0 rather than

Table 3. Barriers to Early Mobilization

Provider Barriers	Solutions
Knowledge	Education; promotion
Fearful attitude	Start small; evolution
Patient sedation	Treat pain and delirium; minimize sedation
Culture of immobility	Find your champions
Unfamiliar professions	Learn to speak their language

moderately sedated (RASS = -2). Physical therapy orders need to go in at the time of admission, not as an afterthought on week 2 of the ICU stay.

Administrators who balk at requests for additional resources will respond to decreased length-of-stay data and decreases in mechanical ventilation days. Management can facilitate having consistent staff in the ICU for improved continuity and team building. Fearful staff can be won over by education from peers who speak their clinical language and by early "wins" by the team of believers.

For example, a common fear is that tubes will fall out during the mobilization process. This has been studied repeatedly and simply does not happen with any significant frequency (≤ 1%).[9] Having a previously critically ill ventilated patient walk through the ICU under her own power on the way home sends a powerful message of positive feedback to resistant staff. Linking improved outcomes to changes in culture is the fastest way to change behavior.

Early mobility for ICU patients is the right thing to do. While there are formidable barriers to successful implementation, the improved patient outcomes that result make it well worth the challenge. ■

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ABSTRACT & COMMENTARY

Recognizing Underuse of Lung-Protective Ventilation in Acute Lung Injury: What Can We Do Differently?

By Betty Tran, MD, MS

Assistant Professor of Medicine, Pulmonary and Critical Care Medicine, Rush University Medical Center, Chicago

Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: Clinical factors associated with underuse of lung-protective ventilation among patients with acute lung injury include older age, shorter height, white race, less severe illness, lower serum bicarbonate levels, shorter ICU stay, and use of non-volume-targeted ventilation.

SOURCE: Walkey AJ, Wiener RS. Risk factors for underuse of lung-protective ventilation in acute lung injury. *J Crit Care* 2012;27:323.e1-9.

Although lung-protective ventilation (LPV) is widely acknowledged as one of the few interventions currently available that improves survival in patients with acute lung injury (ALI), it is poorly adopted in practice. Identification of barriers in utilizing LPV is the first step toward designing interventions that could result in improved patient outcomes in ALI.

Walkey et al conducted a secondary analysis of the Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSNet) trial data from 1995 through 2005 using baseline patient clinical and demographic data before randomization. Of the 1385 study participants with ALI, only 430 (31.2%) received LPV, defined as a tidal volume ≤ 6.5 mL/kg predicted body weight (PBW) based on height and sex. The average tidal volume during pre-enrollment in the study was 7.65 ± 1.82 mL/kg PBW, with a range of delivered tidal volumes being twice that of predicted lung protective tidal volumes.

Factors associated with the underuse of LPV were older age, shorter height, white race, less severe illness (defined by lower Simplified Acute Physiology II and radiographic lung injury scores), lower serum bicarbonate levels, shorter ICU stay prior to study enrollment, and use of non-volume targeted mechanical ventilation. The authors reported similar results in their sensitivity analyses using a tidal volume of ≤ 8 mL/kg PBW, which was used in the ARDSNet trial if patients were breath stacking or dyssynchronous on the ventilator as long as plateau pressures remained < 30 cm H_2O, and using mL/kg PBW as a continuous variable. Notably, the authors observed that tidal volumes of 450 mL for men and 350 mL for women qualified as LPV for more than 80% of both men and women.

■ COMMENTARY

This is the first published study adequately powered to identify risk factors for the underuse of LPV in patients with ALI. Its findings support and expand results from prior smaller studies that identified several factors contributing to the underuse of LPV, including underrecognition of ALI due to perception of patients being less severely ill, difficulties in calculating PBW, and discomfort with untoward effects of LPV (e.g., hypercapnia, hypoxemia, and acidosis).

Although the patient-level risk factors identified in this study are not modifiable per se, their identification highlights common, often unconscious biases in our use of LPV and simple interventions that could improve adherence. First, it is necessary to acknowledge that ALI should be in the differential diagnosis for any patient presenting with acute hypoxic respiratory failure having imaging consistent with diffuse pulmonary edema, regardless of the underlying severity of illness. For those who meet the definition of ALI/ARDS as recently updated in the Berlin Definition,[1] LPV improves outcomes regardless of lung injury severity. Second, increased attentiveness to the ARDSNet protocol, accurate assessments of height, and monitoring of tidal volumes delivered with pressure-targeted ventilation modes are needed in the ICU.

Finally, the development of accessible systematic protocols may improve adherence to LPV by taking decision making out of the hands of the physician, a strategy already shown to be successful in other areas of critical care. Examples include defaulting to lower tidal volumes (450 mL for men and 350 mL for women as suggested by this study) for patients at risk for ALI, attaching charts with precalculated 6 mL/kg PBW tidal volumes and ARDSNet protocols to every ICU ventilator, and incorporating a surveillance system for ALI and LPV use either electronically or as part of ICU rounding checklists. Further studies are needed to confirm whether these interventions will result in improvement of LPV adherence and patient outcomes. ■

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ABSTRACT & COMMENTARY

Can Wearing Earplugs at Night Improve Sleep and Decrease Risk for Confusion?

By Linda L. Chlan, RN, PhD
School of Nursing, University of Minnesota

Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.

SYNOPSIS: Earplug use early in the ICU stay can improve perceived night-time sleep quality and reduce the risk for confusion in patients.

SOURCE: Van Rompaey B, et al. The effect of earplugs during the night on the onset of delirium and sleep perception: A randomized controlled trial in intensive care patients. *Crit Care* 2012;16:R73.

The purpose of this study conducted in the intensive care department of the Antwerp University Hospital in Antwerp, Belgium, was to determine if the application of earplugs to reduce sound (noise) in the ICU during the night could be beneficial in the prevention of delirium. Adult, non-mechanically ventilated ICU patients were enrolled from the 45-bed ICU department. Patients who were expected to stay for a minimum of 24 hours were enrolled early in their ICU stays. Patients were observed for a maximum of 5 nights; they were not receiving any sedation. Patients with known confusion, delirium, dementia, or hearing impairment were not included. Measures included patient clinical data, Richmond Agitation and Sedation Scale, Glasgow Coma Scale, and the Neelon & Champagne Confusion Scale (NEECHAM).

Patients (n = 136) were randomized to either night-time application of ear plugs (n = 69) or no ear plugs (n = 67). An innovative method of blinding ICU staff and data collectors was used by placing a canister at the patient's bedside that either contained the ear plugs or a dummy. The earplugs used in the study were 303 SNR 33 dB(A) manufactured by Howard Leigh Honeywell in San Diego. At 2200 hours, the canister was opened and the earplugs were placed in the patient's ears if they were in the canister. At 0600, the earplugs were removed. Patients and staff were instructed not to report whether earplugs were worn during the night. A blinded researcher collected data from all patients on their sleep perception and performed the delirium assessment using the NEECHAM at 0800, 1600, and 2200 hours. Self-reported sleep perception was assessed in the morning using a set of five questions developed by the researchers.

The patients in each study group were comparable on their clinical characteristics such as illness severity, age, and gender. A majority of the sample were male (66%) with a mean age of 59 years. Many of the patients stayed in the ICU for only 1 night. However, the patients in the earplug group were observed for an average of 43 hours, while the control group was observed for only 33 hours. The NEECHAM assessment divides patients into four categories: delirium, mild confusion, at risk, and normal. Although there was no difference between earplug and control groups with respect to the presence of frank delirium, mild confusion was present in 40% of the control patients vs 15% in the earplug group. More cognitively normal patients were found in the group sleeping with earplugs ($P = 0.006$). In a separate assessment using self-reported sleep quality, patients sleeping with earplugs showed a significantly better sleep after the first night ($P = 0.042$). Nearly half of the study group reported a good sleep, whereas only one-fourth of the control group reported a good sleep.

COMMENTARY

The primary aim of this study was to determine if earplugs could lower the prevalence of delirium and improve sleep perception in critically ill patients. Sleep promoting interventions are understudied in the ICU. Further, the relationship between sleep and delirium is not well articulated. Given the heterogeneous and complex nature of the delirium syndrome, perceived sleep quality with a simple ICU noise reduction intervention may provide a protective benefit for patients at risk for the development of delirium. Despite the small number of patients in this study for more than 2 ICU nights, the results offer important preliminary findings on the benefit of a simple, low-cost intervention to reduce noise and promote sleep quality. Reducing noise during the night is only one intervention to enhance the ICU milieu to promote sleep and reduce risk for delirium.

Other aspects of the environment, such as light exposure, warrant investigation. A multi-milieu enhancement study would shed some light on this complex, severely understudied area.

There was no use of polysomnography to document any physiological benefit from better sleep or whether patients experienced restorative sleep or less interruption of sleep with earplugs. Further, the NEECHAM may not be well known to clinicians, which may limit the transfer of these findings to clinical practice. The findings from this study are limited to short-stay ICU patients only, as most participants were in the study for < 48 hours. It is not known what the benefit may be of using earplugs to reduce noise and promote sleep quality in long-stay ICU patients.

Despite these study limitations, earplugs may be an inexpensive, simple intervention that improves perceived sleep quality and may offer some protective cognitive benefit. ■

ABSTRACT & COMMENTARY

Multidisciplinary Tracheostomy Teams Shorten Time to Decannulation and Increase Speaking Valve Use

By Eric C. Walter, MD, MSc

Pulmonary and Critical Care Medicine, Northwest Permanente and Kaiser Sunnyside Medical Center, Portland

Dr. Walter reports no financial relationships relevant to this field of study.

SYNOPSIS: This systematic review and meta-analysis finds that the implementation of multidisciplinary tracheostomy teams leads to significant improvements in time to decannulation and in speaking valve use but not in ICU or hospital length of stay. The quality of the evidence was low.

SOURCE: Speed L, Harding K. Tracheostomy teams reduce total tracheostomy time and increase speaking valve use: A systematic review and meta-analysis. *J Crit Care* 2012; Aug 27. [Epub ahead of print.]

This systematic review and meta-analysis reviewed studies evaluating the implementation of multidisciplinary tracheostomy teams in acute care hospitals. Potential studies identified and independently reviewed for inclusion criteria related to population studied, intervention, outcomes, and methodology. The population studied included patients with a temporary tracheostomy or undergoing tracheostomy weaning. Studies of patients with tracheostomies related to structural abnormalities of the trachea or with permanent tracheostomy were excluded. The intervention team must have been multidisciplinary and have included at least two health professionals, including one allied health professional (i.e., speech pathologist, physical therapist, or respiratory therapist). Teams comprised of only medicine, or medicine and nursing, were excluded. Seven studies met inclusion criteria. Study quality was judged to be medium to low as all were observational, with a pre-post design, and there were no randomized controlled trials.

The most common outcome measured was time to decannulation, reported in six of seven studies. Sufficient data were reported from four of these studies to perform a meta-analysis. Tracheostomy teams were associated with a reduction in time to decannulation (mean difference 8 days; 95% confidence interval, -6 to -11; $P < 0.01$). Three of the seven studies reported on speaking valve use and all reported increased use from about one-third or less to two-thirds or more of patients using speaking valves. Because a measure of variability was not available for this outcome, meta-analysis could not be performed. Meta-analysis of three studies that reported hospital length of stay (LOS) revealed a decrease in hospital LOS although the result was not statistically significant. A non-significant reduction in ICU LOS was reported in three studies. Insufficient data were available to perform meta-analysis.

■ COMMENTARY

The quality of any meta-analysis is directly related to the quality of included studies. Unfortunately, it has been historically difficult to obtain high-quality data with respect to tracheostomy in critically ill patients. Tracheotomies are performed on only a

minority of critically ill patients making it difficult for any single institution to report outcomes on large numbers of patients, and strong differences of opinion have made multicenter studies challenging. Therefore, despite low-quality studies available for inclusion, meta-analyses such as this study provide useful information for practicing clinicians.

Strengths of this study include careful selection criteria and clinically relevant outcome measures. The authors showed that the introduction of multidisciplinary tracheostomy teams was associated with a statistically significant reduction in time to decannulation. This had been reported in five of the six studies, but small sample sizes limited the ability to report statistically significant outcomes. Tracheostomy teams also appeared to be associated with a greater percentage of patients using a speaking valve. It is not surprising that tracheostomy teams were not associated with a significant reduction in ICU or hospital LOS. LOS is affected by a host of variables, including illness type and severity, a hospital's ability to care for patients with tracheostomies outside of the ICU, and disposition options for these patients. Nevertheless, a shorter time to decannulation and greater use of speaking valves should be highly valued outcomes to both patients and clinicians and argue in support of tracheostomy teams.

However, limitations of this meta-analysis and of the primary studies must be considered. Pre-post intervention studies are considered low grade for valid reasons. A number of changes may occur following an intervention, such as the implementation of a tracheostomy team that may explain the observed outcome. For example, over time improved adherence to low tidal volume ventilation recommendations may decrease lung injury leading to decreased need for long-term tracheostomies.

In summary, the implementation of a multidisciplinary tracheostomy team was associated with a reduction in time to decannulation and an improvement in speaking valve use among critically ill patients with a tracheostomy. While the quality of included studies was low, the findings were generally consistent across studies. The importance of tracheostomy teams may become even more apparent in the future with the growth of percutaneous tracheostomy. As more practitioners perform this procedure, deciding who will follow, and how patients will be followed, will become more important. It makes sense that a dedicated tracheostomy team may help standardize this care and improve outcomes. ■

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PS Form **3526**, October 1999 *(Reverse)*

CME/CNE Questions

1. What percentage of ICU patients should ideally be seen every day by a physical therapist?

a. 1-10%
b. 20-30%
c. 40-50%
d. 60-80%
e. 100%

2. In randomized trials of early mobility, the frequency of dislodgement of lines and tubes was:

a. 1% or less.
b. 10%.
c. 20%.
d. 50%.
e. 70%.

3. Which of the following statements is true regarding the use of lung-protective ventilation in patients with acute lung injury?

a. The vast majority of patients with acute lung injury receive lung-protective ventilation.
b. Physicians are more reluctant to initiate lung-protective ventilation in patients who are already acidotic.
c. Patients on pressure-targeted modes of ventilation are more likely to be receiving lung-protective ventilation.
d. Lung-protective ventilation has only been shown to improve outcomes in severe cases of acute lung injury.
e. Setting tidal volumes at 500 mL would provide lung-protective ventilation to 80% of patients with acute lung injury.

4. Which of the following factors is associated with underuse of lung-protective ventilation in patients with acute lung injury?

a. Shorter stature
b. Decreased severity of illness
c. Younger age
d. Both a and b but not c
e. All of the above

5. The findings of the study by van Rompaey et al demonstrate that the application of earplugs during the night can:

a. increase confusion.
b. increase the incidence of delirium.
c. reduce the risk for developing delirium.
d. increase the risk for developing delirium.
e. None of the above

6. ICU patients in the van Rompaey study who wore earplugs during the night reported:

a. not being able to hear what the staff were asking them.
b. improved perceived sleep quality.
c. diminished perceived sleep quality.
d. experiencing stuffy ears.
e. None of the above

7. The implementation of a multidisciplinary tracheostomy team was associated with:

a. a statistically significant reduction in ICU length of stay.
b. a statistically significant reduction in time to decannulation.
c. improved mortality.
d. less use of a speaking valve.
e. a non-statistical improvement in quality of life.

8. To be included in this analysis, multidisciplinary tracheostomy teams could be defined as:

a. medical professionals only.
b. medical professionals and nurses.
c. at least two or more health professionals, one of whom must be an ear, nose, and throat surgeon.
d. at least two health professionals, including one allied health professional.
e. critical care intensivists only.

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.

[IN FUTURE ISSUES]

Doxycycline to prevent *C. difficile* infection

PHARMACOLOGY WATCH

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Do Benzodiazepines Cause Dementia in the Elderly?

In this issue: Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

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acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

Ginkgo biloba for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■