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Critical Care [ALERT]

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

SPECIAL FEATURE

Evaluation for Extubation

By Dean R. Hess, PhD, RRT

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

Extubation is defined as removal of the endotracheal tube.[1,2] The decision to extubate is usually based on three considerations: 1) need for invasive respiratory support; 2) patency of the upper airway; and 3) ability to clear secretions from the lower respiratory tract. The clinical decision to extubate is not trivial. Mortality is higher in patients who require re-intubation within 24-72 hours after extubation. However, prolonged intubation is also not benign and can increase the risk of nosocomial pneumonia, upper airway injury from the tube, and ventilator-induced lung injury.[1,2] This essay will take a critical look at the evaluation for extubation.

VENTILATOR LIBERATION

A daily spontaneous breathing trial (SBT), perhaps coupled with a spontaneous awakening trial, is now standard practice to identify whether a patient can be liberated from mechanical ventilation.[3] However, the increasing use of non-invasive ventilation (NIV) has changed the actions we might take if a patient passes or fails an SBT. Some patients who fail an SBT might be extubated directly to NIV. Other patients who pass an SBT, but are at risk for extubation failure, might also be extubated directly to NIV. Note that in both of these scenarios, patients are extubated directly to NIV. This is in contrast to the use of NIV to rescue a failed extubation, which is not supported by randomized controlled trials.

Burns et al performed a meta-analysis of five randomized controlled trials of NIV to facilitate weaning from mechanical ventilation[4] — in other words, earlier extubation directly to NIV. They found that extubation to NIV was associated

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with lower mortality, less ventilator-associated pneumonia, shorter course of mechanical ventilation, shorter ICU stay, and shorter hospital stay. Because more than 80% of the patients in these studies had COPD, it is unknown whether the benefit is limited primarily to patients with COPD. Epstein recommends the following criteria when considering the use of NIV for early extubation:[5] 1) the patient must be able to breathe spontaneously for at least a short period; 2) the patient should be able to adequately clear secretions; 3) the patient should be able to tolerate the interface and to breathe spontaneously for at least 5-10 minutes to allow for necessary mask and ventilator adjustments; 4) NIV is strongly discouraged if the patient would be technically difficult to re-intubate.

Three randomized controlled trials support that NIV is effective when used immediately after extubation in patients at high risk for extubation failure.[6-8] Risk factors for extubation failure in these studies were age greater than 65 years, cardiac failure as the cause of intubation or chronic heart failure, APACHE-II score greater than 12 on the day of extubation, more than one consecutive failed SBT, $PaCO_2$ > 45 mm Hg, more than one comorbidity (excluding chronic heart failure), weak cough, and stridor at extubation not requiring immediate reintubation. With the possible exception of COPD exacerbation, NIV should not be used routinely after extubation or in established post-extubation respiratory failure.

AIRWAY PROTECTION

No clinician will debate the prudence of keeping the endotracheal tube in place if upper airway obstruction were to occur in the absence of the tube. Likewise, no rational clinician recommends extubation for a patient at risk for aspiration of upper airway secretions or gastric contents. The challenge is to identify patients at risk.

Poor mental status is commonly given as a reason why patients who pass an SBT are not extubated, the reason being concerns of airway protection. In neurosurgical patients, Namen et al reported that the odds of successful extubation increased by 39% with each Glascow Coma Score (GCS) increment.[9] A GCS ≥ 8 at extubation was associated with success in 75% of cases vs a success rate of 33% for a GCS < 8.[10]

These results are at odds with those of Coplin et al, who explored the implications of extubation delay in brain-injured patients.[11] They found that timely extubation in this patient population was safe. Although patients with worse neurologic condition had more delay, some patients with good neurologic condition were kept intubated after meeting extubation readiness criteria and some patients in coma were successfully extubated. Patients were successfully extubated despite absent cough, gag, or increased suctioning needs. Extubation delay was associated with morbidity and mortality. The authors concluded that this study does not support delaying extubation when impaired neurologic status is the only concern prolonging intubation. My personal observation has been that poor mental status is commonly used as justification not to extubate when members of the team are opposed to extubation for whatever the reason may be.

Some intubated patients with poor mental status also have difficulty handling upper airway secretions and are clinically observed to drool their oral secretions. In such patients, concern about aspiration of oral secretions after extubation is reasonable. Although this has not been investigated to my knowledge, it might be reasonable to delay extubation in patients with difficulty handling upper airway secretions.

UPPER AIRWAY EDEMA

Airway obstruction due to laryngeal edema following extubation occurs in 3%-30% of patients, of whom < 5% require re-intubation.[12] A cuff-leak test is often used to screen for

upper airway obstruction before extubation. To perform this test, the cuff of the endotracheal tube is deflated and the air leak around the tube through the upper airway during positive pressure ventilation is assessed. Absence of a leak, or a small leak, suggests upper airway obstruction. The result of the test can be expressed qualitatively, presence or absence of leak, or quantitatively, in which the difference between inhaled and exhaled tidal volume is measured.

Ochoa et al conducted a systematic review and meta-analysis to assess the diagnostic accuracy of the cuff leak test.[12] The analysis included 11 studies and 2303 patients. The overall positive likelihood ratio for upper airway edema (no leak) was 5.9 and the overall negative likelihood ratio (leak) was 0.48. Only three studies were included for the outcome of re-intubation. The overall positive likelihood ratio for re-intubation (no leak) was 4.04 and the overall negative likelihood ratio (leak) was 0.46. If we take a pre-test probability for upper airway edema of 15%, the post-test probability is increased to 51%. With a negative likelihood ratio (presence of leak) of 0.48, the post-test probability fell to 8%. For a reported incidence of re-intubation secondary to upper airway obstruction of 5%, the absence of leak increases the probability for re-intubation to 17%, and the presence of leak decreases the probability for re-intubation to 2%.

The results of this meta-analysis suggest that the presence of a positive cuff-leak test (absence of leak) is suggestive of a higher risk of upper airway obstruction and re-intubation.[12] On the other hand, the presence of a detectable leak has a low predictive value and does not rule out the occurrence of upper airway obstruction or the need for re-intubation. A reasonable recommendation might be to reserve the leak test for patients with high pre-test probability such as those with difficult intubation or other clinical reasons to suspect upper airway edema. In such patients who have a positive leak test (no leak), it would be reasonable to delay extubation and administer a short course of methylprednisolone before extubation.[13]

COUGH AND SECRETIONS

One of the functions of the endotracheal tube is to provide a conduit for suctioning and bronchoscopy. A legitimate consideration before extubation is whether the patient can adequately clear airway secretions.

Khamiees et al evaluated potential predictors of extubation outcome in patients who have successfully completed an SBT.[14] Cough strength was measured with a semi-objective scale of 0 to 5; the magnitude of endotracheal secretions was measured as none, mild, moderate, or abundant; and patients were asked to cough onto a white card held 1-2 cm from the endotracheal tube. If secretions were propelled onto the card, it was termed a positive white card test result. They found that there was synergism between poor cough strength and abundant endotracheal secretions in predicting extubation failure.

In a follow-up study, Smina et al evaluated cough peak flow and extubation outcomes.[15] After patients passed an SBT and extubation was being considered, they were asked to cough into a peak flow meter connected to the endotracheal tube. The volume of endotracheal secretions suctioned 2-6 hours prior to extubation was measured. Interestingly, the magnitude of endotracheal secretions was not associated with the outcomes assessed. But patients with a cough peak flow < 60 L/min were five times more likely to be unsuccessfully extubated and were 19 times as likely to die during the hospital stay.

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Salam et al evaluated neurologic status, cough, secretions, and extubation outcomes.[16] Patients who were unable to complete four simple tasks

(open eyes, follow with eyes, grasp hand, stick out tongue) were more than four times as likely to fail as those who completed these commands. There was synergistic interaction between these risk factors; failure rate was 100% for patients with all three risk factors (poor neurologic status, cough, and secretions) compared to 3% for those with no risk factors. Patients who failed a trial of extubation were nearly four times as likely to have any two risk factors compared to those who were successful. Those with a cough peak flow ≤ 60 L/min were nearly five times as likely to fail extubation. Patients with secretions of more than 2.5 mL/hr were three times as likely to fail.

Su et al induced a cough in inbutated patients by instilling 2 mL of saline at the end of inspiration and measuring cough peak flow using a hand-held respiratory mechanics monitor.[17] In a multivariate analysis, they found that involuntary cough peak flow and APACHE II were the primary predictors of extubation success in critically ill patients who passed an SBT.

These studies are commonly discussed in the context of assessing extubation readiness. To my knowledge, however, these results have never been replicated and measurement of cough peak flow and quantitative measures of secretion volume are not used commonly in everyday practice. But these studies do support that cough strength and secretion volume are important considerations in the decision to extubate. I think it is important to evaluate both cough and secretions. For example, a patient with copious secretions and who also has a strong cough may adequately clear the airway after extubation. Similarly, a patient with a weak cough but minimal airway secretions may do well after extubation. The patient with a weak or absent cough and copious secretions is at greatest risk for extubation failure.

The cough-assist device (mechanical in-exsufflator) is used to assist cough and airway clearance in patients with neuromuscular disease.[18] However, it has not been commonly used in the ICU. A case might be made for its use post extubation, given that many mechanically ventilated patients have generalized weakness. It is possible that post-extubation use of NIV and the cough-assist device might prevent extubation failure in patients with a weak cough. This deserves appropriate study in a randomized controlled trial.

SUMMARY

Clinicians should separate the need for mechanical ventilation from the need for an endotracheal tube. Before extubation, the ability to clear secretions and protect the airway should be assessed. The use of NIV and the cough-assist device may allow extubation of some patients who otherwise might require prolonged intubation or tracheostomy. ■

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ABSTRACT & COMMENTARY

Early Aggressive Therapy to Reduce Serum Lactate Levels Improves Outcomes in Critically Ill Patients

By David J. Pierson, MD, Editor

SYNOPSIS: In a multicenter study, critically ill patients with initial hyperlactatemia had improved outcomes (including shorter ICU stays and lower adjusted mortality) compared to control patients when they were managed for the first 8 hours with a resuscitation protocol targeted at reducing the lactate level by at least 20% every 2 hours.

SOURCE: Jansen TC, et al; LACTATE study group. Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med 2010;182:752-761.

Carried out in four ICUs in the Netherlands, this study evaluated the effects of a serum lactate-guided resuscitation protocol during initial management of critically ill patients with elevated lactate levels, as compared to standard management not guided by serial lactate measurements. Adult patients with admission lactate levels of 3.0 mEq/L or greater were enrolled during a 2-year period. Patients with conditions that might either generate more lactate (such as grand mal seizures) or affect its clearance (such as severe liver disease) were excluded. Patients were randomized on admission to the ICU, and were managed either according to the protocol or without serum lactate guidance for the initial 8 hours; thereafter, their management was according to the judgment of their treating intensivists.

Patients in the control group had management targeted at a mean arterial pressure > 60 mm Hg, heart rate < 100/min, central venous pressure 8-12 mm Hg (12-15 mm Hg in ventilated patients), urine output at least 0.5 mL/kg/hr, hemoglobin at least 7 g/dL, and arterial oxygen saturation at least 92%. In this group, central venous oxygen saturation ($ScvO_2$) monitoring was allowed at the discretion of the managing intensivist, but lactate levels were not made available during the 8-hour intervention period. In the intervention (lactate-guided) group, the above management goals were the same, with the addition of a targeted reduction in serum lactate of at least 20% every 2 hours until the level was 2.0 mEq/L or less, and the goal of achieving and maintaining a $ScvO_2$ value of at least 70%. Arterial blood was preferentially used for lactate measurement, but the use of venous or capillary blood was also allowed; measurement was by means of a hand-held point-of-care device (Accutrend®, Roche Diagnostics; Mannheim, Germany), which was provided for the study by the manufacturer.

There were 177 patients in the control group and 171 patients in the lactate-targeted group. Their ages, demographics, admission diagnoses, APACHE II scores (mean ~23), and sequential organ failure assessment (SOFA) scores (mean ~9) were comparable. Most of the patients were admitted to the ICU within 6 hours of hospital admission, and median time from ICU admission to randomization was less than 1 hour. The lactate group received more fluids and vasodilators, although there were no differences between the groups with respect to the patients' lactate levels themselves. Hospital mortality in the control group was 43.5% as compared to 33.9% in the lactate group, a nonsignificant difference ($P = 0.067$). However, when adjusted for predefined risk factors, mortality was lower in the lactate group (hazard ratio, 0.61; 95% confidence interval, 0.43-0.87; $P = 0.006$). SOFA scores were lower between 9 and 72 hours after starting the study in the lactate patients; they also had fewer hours of vasopressor therapy, shorter periods of mechanical ventilation, and shorter ICU stays. The authors conclude that lactate-guided initial fluid and hemodynamic management among critically ill patients with initial hyperlactatemia is beneficial.

COMMENTARY

In this multicenter, open-label randomized controlled study, the use of a serum lactate-guided resuscitation protocol during the initial 8 hours in the ICU, aimed at reducing lactate levels by at least 20% every 2 hours until they were 2 mEq/L or less, reduced ICU length of stay and also — after adjustment for various factors — both ICU and hospital mortality. Although

the mechanism is unclear, blood lactate levels correlate inversely with prognosis in critically ill patients, irrespective of the type of critical illness or the presence of either shock or organ failure. Attention has thus naturally focused on the possible effects on patient outcomes of measures to reduce serum lactate, particularly in the early hours of treatment for critical illness. Current evidence indicates that mortality relates to the primary disease process generating the increased serum lactate (primarily through tissue hypoxia) rather than the lactate molecule itself, and reducing lactate levels by infusing dichloroacetate does not reduce mortality.

Although the setting was somewhat different and only about 40% of the patients had severe sepsis or septic shock, this study supports the findings of the widely heralded, single-center, emergency department study of Rivers et al in patients with sepsis,[1] which has been used as the basis for broad application of early goal-directed therapy in critically ill patients. The findings of Jansen et al will likely be used to support wider use of lactate monitoring in the ICU, in addition to the use of $ScvO_2$ monitoring and the hemodynamic and other components of early goal-directed therapy for severe sepsis and septic shock.

If past critical care experience is any guide, these things may also begin to be used in clinical settings different from those in which the results were obtained. Based on its findings, the current study supports a lactate-guided strategy of fluid and hemodynamic management in critically ill patients starting immediately on presentation to the ICU and continuing for the next 8 hours. Whether additional benefit might accrue from the use of this strategy beyond 8 hours, or if it is initiated later in the course of the patient's illness, is unknown and must await the results of additional studies. ■

Reference

1. Rivers E, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-1377.

ABSTRACT & COMMENTARY

Feasibility of Early Mobilization Therapy in Mechanically Ventilated Patients

By Richard J. Wall, MD, MPH

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

SYNOPSIS: This study provides a detailed description of the successful mobilization protocol, including barriers and complications, used in a recently published randomized trial.

SOURCE: Pohlman MC, et al. Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. Crit Care Med 2010;38:2089-2094.

Intensive care unit (ICU) survivors experience various morbidities that can limit long-term recovery. One of the most common problems, neuromuscular weakness, has been linked to substantial and lasting decrements in quality of life. In recent years, researchers have started exploring the utility of "early mobilization" (i.e., physical therapy while still in the ICU) to counteract this problem.

In a 2009 landmark study, early mobilization of mechanically ventilated patients led to improved functional independence, more ventilator-free days, and reduced ICU delirium.[1] Patients were randomized either to the intervention of early physical/occupational therapy (PT/OT) or to usual care.

The results were impressive. A return to independent functional status by hospital discharge was seen in 59% of the intervention arm vs 35% of controls ($P = 0.02$). Patients in the intervention group also had shorter median duration of delirium (2 days vs 4 days; $P = 0.02$),

Table 1. Contraindications to initiating PT/OT

- Mean arterial pressure < 65 mm Hg
- Heart rate < 40 or > 130 beats/min
- Respiratory rate < 5 or > 40 breaths/min
- Pulse oximetry < 88%
- Evidence of elevated intracranial pressure
- Active gastrointestinal bleeding
- Active myocardial ischemia
- Actively undergoing procedure
- Agitation requiring increased sedatives in past 30 min
- Insecure airway device

Table 2. Adverse events: Contraindications to continuing PT/OT

- Mean arterial pressure < 65 mm Hg
- Heart rate < 40 or > 130 beats/min
- Respiratory rate < 5 or > 40 breaths/min
- Pulse oximetry < 88%
- Marked ventilator dysynchrony
- Patient distress, combativeness
- New arrhythmia
- Concern for myocardial ischemia
- Concern for airway device integrity
- Fall to knees
- Endotracheal tube removal

and more ventilator-free days (24 vs 21 days; $P = 0.05$).

Although the authors described complication rates as low, lingering concerns remained for many of us who were trying to translate these findings into practice in our own ICUs.

In the current study, the authors offer a more detailed glimpse at what actually occurred in the intervention arm (n = 49 intubated patients). First, patients were screened for contraindications to initiating PT/OT *(see Table 1, above)*. A protocol ensured that patients underwent daily sedative interruption unless neuromuscular blocking agents were being administered. To be considered "wakeful" a patient was required to follow at least three of four commands: open eyes to voice, track with eyes, squeeze hand on request, protrude tongue on command. On meeting wakefulness criteria, therapy was initiated. All medical devices were assessed and properly positioned before the session. The article describes the preparatory steps and various exercises employed in detail. Patients were reassessed each day.

Overall, early PT/OT occurred at a median of 1.5 days after intubation. On average, therapy sessions lasted 26 minutes. Sedative infusions were stopped before therapy in 83% of patients. The majority of intubated patients were able to perform extremity exercises (85%), actively move in bed (76%), sit at the edge of bed (69%), simulate eating (67%), and groom themselves (64%). A substantial number of sessions saw patients move from bed to chair (33%) or stand (33%). Ambulation occurred in 15% of sessions (median, 15 feet).

"Potential barriers" were identified in 58% of sessions. For example, 35% of sessions had FiO_2 of ≥ 0.6, a single vasopressor running in 17%, and two vasopressors running in 14%. Central venous catheters were present in 75%, arterial lines in 47%, dialysis catheters in 18%, and 37% of patients were obese (body mass index > 30 kg/m^2). Delirium was seen in 53% of patients. Continuous renal replacement occurred during 9% of sessions. Among intubated patients, therapy was withheld in 26 of 270 eligible sessions. The most common reasons were ventilator dysynchrony (n = 20), blood pressure drop (n = 4), and active gastrointestinal blood loss (n = 2).

Despite a high number of potential barriers, adverse events led to discontinuation of therapy in only 16% of sessions *(see Table 2, above)*. These included desaturation (6%), heart rate increase (4%), ventilator dysynchrony (4%), agitation/discomfort (2%), and device displacement (0.8%). Four devices were displaced without harm to patient (arterial line, rectal tube, nasogastric tube, and transient disconnection of ventilator circuit). Agitation after sedative interruption, requiring stopping therapy and resedation, occurred in < 10% sessions.

COMMENTARY

Not surprisingly, a majority of critically ill patients have perceived "barriers" to early mobilization. According to the results of this study, however, adverse events resulting from those barriers are not a big problem. In this study, no patient was extubated, no central

venous catheter was lost, and no serious arrhythmias ensued.

Nonetheless, perceived barriers are relevant because they can ultimately determine whether clinicians are willing to adopt protocols and follow through on actions. When an organization implements an early mobilization protocol, they would be wise to periodically audit the process, ensure goals are being met, survey staff, and feed those data back to frontline clinicians.

In my opinion, the real obstacle to early mobilization isn't lines, tubes, and drains. Rather, it's the rampant oversedation and delirium seen in mechanically ventilated patients. It makes little sense for an ICU to implement an early mobilization protocol if they don't have a working "sedation vacation" protocol in place. If a patient is unresponsive and unable to follow commands, PT/OT sessions will merely consist of passive range-of-motion exercises.

To be successful, an early mobilization protocol requires continuous interdisciplinary coordination between nurses, physicians, clinical pharmacists, respiratory therapy, and PT/OT. An early mobilization protocol is not a simple plug-play-and-walk-away add-on for the ICU. ■

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CME/CNE Questions

29. Which of the following should be assessed before extubation?

a. Ventilator liberation
b. Upper airway edema
c. Cough strength
d. Quantity of secretions
e. All of the above

30. Which of the following statements is *true* about the study of lactate-guided fluid and hemodynamic management in critically ill patients?

a. The lactate-guided protocol reduced overall, all-cause mortality.
b. Serum lactate levels were significantly lower in patients managed with the lactate-guided protocol.
c. The intervention was used only for the initial 8 hours in the ICU.
d. None of the above

31. Which of the following was a common reason for discontinuing mobilization in mechanically ventilated patients?

a. Unexpected extubation
b. Arrhythmia
c. Family protest
d. None of the above was common

Answers: 29. e, 30. c, 31. d.

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]

Serum sodium levels to prognosticate in patients with pulmonary embolism

Effects of nebulized heparin in critically ill patients

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Rivaroxaban: Another Warfarin Replacement

In this issue: Rivaroxaban may be dabigatran's first competitor; a new way to measure non-adherence to medication therapy; FDA Actions.

Another Warfarin Replacement on Horizon

Just as Boehringer Ingelheim begins marketing dabigatran (Pradaxa®) as a replacement for warfarin, a competitor drug may be on the horizon. As reported at the American Heart Association (AHA) meetings in November, rivaroxaban, an oral drug factor Xa inhibitor, is as effective as warfarin at preventing stroke and blood clots in patients with nonvalvular atrial fibrillation.

The ROCKET AF study (Stroke Prevention Using the Oral Direct Factor Xa Inhibitor Rivaroxaban Compared With Warfarin in Patients with Nonvalvular Atrial Fibrillation) looked at more than 14,000 patients with atrial fibrillation. Patients were randomized to warfarin or rivaroxaban (20 mg/day). The time in therapeutic range for warfarin was 57.8%. With a primary endpoint of stroke and non-CNS systemic embolism, rivaroxaban was associated with a rate of 1.71 events per 100 patient-years vs 2.16 for warfarin (P = 0.015 for superiority and P < 0.001 for non-inferiority). On an intention to treat (ITT) basis, event rates were 2.12 for rivaroxaban vs 2.42 for warfarin (P = 0.117). There were 55 intracranial bleeds with rivaroxaban compared with 84 with warfarin (P = 0.019). Rivaroxiban also showed numerically fewer MIs (0.91 vs 1.12 per 100 person-years; P = 0.12). All-cause mortality was 1.87 in the rivaroxaban group vs 2.21 in the warfarin group (P = 0.073). In the ITT analysis, mortality was 4.52 vs 4.91 (P = 0.152), respectively.

This study (presented at the American Heart Association Scientific Sessions; Chicago, IL; Nov. 15, 2010) was the seventh Phase III trial in the development of rivaroxaban, with other studies evaluating the drug for prevention and treatment of venous thromboembolism, indications that Bayer and Johnson & Johnson have already filed with the FDA. It is also expected that a new drug application will be filed soon for the prevention of stroke in patients with nonvalvular atrial fibrillation. Like dabigatran, rivaroxaban requires no monitoring and has few drug interactions. Rivaroxaban has the advantage of being dosed once a day compared to twice-daily dosing for dabigatran. ■

Non-adherence: A New Way to Measure

A new study examines drug adherence in an interesting way — by looking at the rate of prescriptions abandoned at the pharmacy. Traditional non-adherence studies have looked at refill rates, pill counting, and patient reports of medication use. But prescriptions abandoned at the pharmacy represent a potential opportunity to intervene and improve adherence at the very onset of the prescribing process.

Researchers used the CVS pharmacy database to evaluate more than 10 million prescriptions

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

filled by more than 5 million patients. The overall abandonment rate was 3.27%, although nearly half of those were eventually filled by the same drug or a similar drug within 30 days. Not surprisingly, patients were least likely to abandon opiate prescriptions, and were most likely to abandon expensive prescriptions. Prescriptions with a copayment of $40-$50 and those with a copayment of more than $50 were 3.4 times and 4.68 times more likely to be abandoned, respectively, than prescriptions with no copayment ($P <$ 0.001 for both comparisons). New users of medications were more likely to abandon prescriptions than prevalent users, and prescriptions that were delivered to the pharmacy electronically were 1.64 times more likely to be abandoned than those that were not electronic ($P < 0.001$); however, they were unable to determine whether written prescriptions were never delivered to the pharmacy by patients.

The authors concluded that prescription abandonment represents an important opportunity to intervene and improve adherence (*Ann Intern Med* 2010;153:633-640). An accompanying editorial points out that the rate of abandonment in this study was actually quite low. Others studies have suggested that 17%-20% of patients do not pick up new prescriptions, and 8% of patients' prescriptions are denied by health plans. Physicians and pharmacists are urged to remain mindful that costs are an important barrier to adherence and that lower cost alternatives should be prescribed "whenever feasible" (*Ann Intern Med* 2010;153:680-681). ■

FDA Actions

The FDA has asked the manufacturers of propoxyphene-containing pain medications (Darvon®, Darvocet®, and generics) to withdraw them from the market. The withdrawal is based on new data showing the drugs are associated with serious and fatal heart arrhythmias. Health care professionals are advised to stop prescribing propoxyphene and patients are asked to contact their health care providers to discuss switching to other pain medications. Propoxyphene has been the target of consumer groups for more than 30 years because of evidence of poor efficacy in treating pain and a high level of side effects including falls. ■

The FDA has approved duloxetine (Cymbalta®) for the treatment of chronic musculoskeletal pain. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, was previously approved for treating depression, generalized anxiety disorder, diabetic neuropathy, and fibromyalgia. The new indication for musculoskeletal pain includes low back pain and osteoarthritis. The expanded indication was based on the results of four double-blind, placebo-controlled trials, which showed that patients treated with duloxetine had significantly greater pain reduction than those patients treated with placebo. Duloxetine is marketed by Eli Lilly and Company. ■

The FDA has approved lurasidone for the treatment of schizophrenia in adults. The drug is classified as an atypical antipsychotic, and like other drugs in this class, carries a boxed warning regarding an increased risk of death associated with off-label use to treat behavioral problems in older adults with dementia. Common adverse reactions include drowsiness, feelings of restlessness, nausea, agitation, and Parkinsonian symptoms such as bradykinesia, tremor, and muscle stiffness. Lurasidone will be marketed by Sunovion Pharmaceuticals as Latuda™. ■

The FDA has approved a new injectable cephalosporin, ceftaroline, to treat community-acquired bacterial pneumonia (CABP) and bacterial skin infections, including those caused by methicillin-resistant *Staphylococcus aureus*. Ceftaroline was approved based on data from four studies that showed the drug to be as effective as ceftriaxone for the treatment of CABP and as effective as vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections. The recommended dose for patients with normal renal function is 600 mg given as a one-hour IV infusion every 12 hours. Ceftaroline is marketed by Forest Laboratories as Telflaro™. ■

The FDA's Vaccines and Related Biological Products Advisory Committee has recommended an expanded indication for Gardasil®, Merck's quadravalent human papillomavirus vaccine to prevent anal intraepithelial neoplasia and anal cancer in males and females ages 9-26. The approval was based on a phase III double-blind, placebo-controlled trial in which more than 4000 males were randomized to receive the three-dose vaccine or placebo. There was a significant reduction in the rate of anal intraepithelial neoplasia or anal cancer, especially in men who have sex with men. The vaccine is already approved for prevention of genital warts and cervical, vulvar, and vaginal cancer in females ages 9-26 and prevention of genital warts in males ages 9-26. ■