CRITICAL CARE ALERT®

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

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INSIDE

Visiting Hours in the ICU: Too Restrictive? Too Liberal?

ABSTRACT & COMMENTARY

Synopsis: *In this article, a leading expert in the area of improving health care quality argues that restricting visiting hours in ICUs is neither caring, compassionate, nor necessary.*

Source: Berwick DM, Kotagal M. *JAMA*. 2004;292:736-737.

In this commentary, Berwick and Kotagal list 3 common reasons for restricting ICU visiting hours. They are: frequent visits by family members and others induce physiologic stress for the patient; such visits create barriers to the effective provision of care; and they lead to exhaustion on the part of those who visit. Berwick and Kotagal examine the rationale and implications of each, and argue that none of them justifies restricting the access of family and friends to their critically ill loved ones. They conclude that "hospitals should open their ICUs, ask their patients and families, their nurses, and their physicians what works, assess the effect of these changes openly and objectively, and move toward a defined but unrestricted ICU visitation policy."

Among their suggestions for improving communication between caregivers and family members, and thus reducing the friction that frequently develops around ICU visitation, are beepers so that the family can be contacted if there is a change in the patient's condition; automated, secure phone messages updated with changes in the patient's condition; and regularly scheduled updates from the managing physician.

COMMENT BY JAMES E. McFEELY, MD

We are all aware that there is frequently tension between hospital staff and patients' families around the issue of limited visiting hours in the intensive care unit. Frequently, this tension is directly proportional to the severity of illness of the patient. In this article, Berwick, chief executive of the Institute for Healthcare Improvement, a well-known nonprofit organization with a focus on improving quality in healthcare, suggests that restrictions on visits in the ICU are unnecessary. He cites 3

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areas of concern, and argues that they are either overestimated or on balance negated by the benefits to the patient.

I certainly agree with Berwick that, where possible, patients should be allowed to participate in decision-making with regard to deciding who is able to visit them and for how long. It is with the patients who are too ill to be able to participate in this decision-making that the tension most frequently arises. In our institution, we have experimented with both a closed, fixed schedule of hourly visiting times for short periods of time, as well as with a more open visitation schedule, and have frankly found problems with both. Some patients' family members have complained of a circus-like atmosphere during the open visitation schedule, with large numbers of people coming and going and, in the family member's opinion, interfering with the care of the patient. Other patients' families complain that the fixed visiting schedule they were given does not provide enough access to their loved ones.

Most of the time, having a patient's family in the room probably benefits the patient in terms of reduction in physiologic stress, though we have all seen examples to the contrary. However, and I think in those particular instances, restricting visiting, at least for the individual causing the additional stress, is probably in the patient's best interest. Systems can be set up to minimize family intrusion in terms of the provision of care, and we have found most individuals are quite accommodating when this is explained to them. It is also true that family and friends are at risk of fatigue and exhaustion, particularly early in the course of a very critically ill patient. I frequently tell patients' families that what they are experiencing is more akin to a marathon than to a sprint, and I try to assist them in developing a routine that will allow them to spend time away from the hospital and give themselves respite. Things that can help in this regard include having 24-hour phone access to the patient's nurse, giving beepers to patients' families so they may be contacted about changes in the patient's condition, having a secure, updated phone message that patients' families can access to retrieve information at their convenience, and having a relatively fixed schedule of updates from the patients' care providers, and in particular from the physician manager.

Minimizing areas of tension between the patient's family and the health care team is an important goal in the provision of care. One of the frequent areas of conflict is over visiting hours. In general, the goal of minimizing restrictions to visitors is a good one; but it can be a two-edged sword. I encourage all of us to evaluate our current visiting policies in an attempt to make them as family friendly as possible, taking into consideration those factors most relevant to the individual ICU, including the physical constraints of the unit, the types and the number of patients cared for, and the ancillary resources available to both hospital staff and families. ■

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Intra-Hospital Transport of ICU Patients: Traveler Beware!

ABSTRACT & COMMENTARY

Synopsis: *In this study of anonymously reported adverse occurrences related to intra-hospital transportation of critically ill patients, problems were related to equipment in 39% and to patient/staff management issues in 61%; 31% of the incidents had serious adverse outcomes.*

Source: Beckmann U, et al. *Intensive Care Med*. 2004;30:1579-1585.

THIS COLLABORATIVE CROSS-SECTIONAL STUDY BY Beckmann and colleagues at Johns Hopkins and John Hunter Hospitals, the latter in Newcastle, NSW, Australia, examined incident reports relating to the intra-hospital transport of ICU patients that were submitted to the Australian Incident Monitoring Study in Intensive Care from 1993 through 1999. Any ICU staff member could submit a report, which was anonymous and voluntary.

Of more than 11,000 incidents described in 7525 individual reports from 93 ICUs during the study period, 176 reports (191 incidents) from 37 ICUs concerned incidents that occurred during transportation within hospital. They classified the 191 incidents into equipment problems (75 cases, 39%) and patient/staff management issues (116 cases, 61%). Common equipment-related problems involved access to elevators (18 incidents), drug delivery systems (18), battery/power supply (14), monitors (12), intubation equipment (7), transport ventilators (4), and oxygen supply (3). Common patient-staff management problems included communication/liaison, airway management (securing; accidental extubation; unplanned reintubation), vascular line use, patient monitoring and positioning, and set-up of equipment.

Most incidents occurred en route to or from the operating room (36%), the radiology department (35%), a hospital ward (12%), or the emergency department (9%). In 61 cases (35%), the transport occurred as part of the initial ICU admission; in 78 (44%) it occurred during on-going ICU care, and in 14 (8%) during an emergency intervention.

Significant adverse outcomes occurred in 59 cases (31%). These included major physiological derangement (26 cases), patient/relative dissatisfaction (12), prolonged hospital stay (7), physical or psychological injury (6), and death (4).

Factors contributing to the incident during transport were classified as system-based factors (such as work practices, equipment problems, and aspects of the physical environment infrastructure) in 46%, and human-based factors (errors related to knowledge, hospital rules, skills, or technique) in 54% of cases. Equipment-related incidents were felt to be due to communication problems, inadequate protocols, inservicing or other training, or the equipment itself. Management-related incidents were most commonly errors of problem recognition and judgment, failure to follow protocols, inadequate patient preparation, haste, and inattention. They conclude that intra-hospital transport poses an important risk to ICU patients, that standards are needed, and that monitoring of incidents occurring in this context is important.

COMMENT BY DAVID J. PIERSON, MD

Transporting a critically ill patient from the ICU to another area of the hospital for a surgical procedure or diagnostic study is a dangerous undertaking. This is clear to anyone who cares for such patients, and has also been documented in numerous studies. This study sheds light on the types of incidents that happen commonly, and some of the factors associated with them. It demonstrates that transport-related adverse incidents are a complex problem. Lots of different things can go wrong, and for lots of different reasons. Minimizing transport-related problems is one of the major challenges facing both clinicians and administrators in today's practice of critical care.

This study has a number of limitations. The database used relies on voluntary, anonymous incident reports, whose accuracy can seldom be verified. Submitted reports undoubtedly underestimate the true incidence of the events being examined, and there are likely a variety of selection and reporting biases at work. However, despite these limitations, which the authors acknowledge, this study's findings are important as reminders of the frequency, variety, and seriousness of transport-related adverse incidents.

This study has another important implication for clinicians. Being in the ICU is dangerous for patients, but taking them away from it to have something done in another part of the hospital is probably even more so. Therefore, the reason for the trip needs to be pretty important. While there is no question that many surgical interventions and diagnostic procedures are both necessary and emergent, some transports can probably be delayed until conditions are optimized, combined with trips for other procedures, or avoided altogether. Recognizing that moving patients to other parts of the hospital is often unavoidable, making sure that they are not taken from the resources and stability of the ICU unless this is truly necessary is one of the greatest challenges in the practice of critical care medicine. ■

ACE-Inhibitor Angioedema: How Common? How Serious?

ABSTRACT & COMMENTARY

Synopsis: *During a 5-year period, 45 patients were admitted to an inner-city teaching hospital with angioedema caused by angiotensin-converting inhibitor medications, and 18 (40%) of them required ICU admission for potential upper-airway compromise.*

Source: Sondhi D, et al. Chest. 2004;126:400-404.

In this retrospective study from a community teaching hospital in Philadelphia, Sondhi and colleagues identified all patients whose admissions had been assigned the diagnosis code for angioedema (AE) during the 5 academic years starting in 1996. They reviewed these patients' medical records to determine the presenting symptoms and signs, treatments and outcomes, as well as whether the patients were taking angiotension-converting enzyme inhibitors (ACEIs) when they developed symptoms. All patients on ACEIs were assumed to have ACEI-induced AE. During the 5-year study period, 70 patients were admitted with AE, among whom this was considered related to ACEI therapy in 45 (64%). In the other 25 patients, AE was ascribed to food allergy, antibiotics, or infection in 23. No precipitating factor could be identified in 2 cases.

Of the 45 patients with ACEI-related AE, the mean age was 62 years and 41 (91%) were African American. Twenty nine (67%) were women. No specific ACEI appeared more likely to cause AE than the others. Duration of ACEI use prior to presentation ranged from 1 day to 5 years; 21 of 45 (45%) patients presented within 2 months of starting the drug, while 11 (24 patients) had been on it for 6 months to 5 years.

Presenting symptoms and signs are shown in the Table. All patients were treated in the emergency department with H1 blockers, methylprednisolone, and intravenous fluids, and 15 of them received epinephrine. 18 patients (40%) were admitted to the ICU, and 5 (28% of those requiring intensive care) required intubation, one of whom underwent emergency cricothyrotomy. Mean duration of intubation in these patients was 2.2 days, and patients admitted to the ICU spent an average of 2.2 days there. Care in the ICU was supportive. There were no deaths or serious complications in the study cohort.

COMMENT BY DAVID J. PIERSON, MD

Angioedema produces asymmetrical, non-pitting edema of the skin and mucus membranes. Typically presenting with facial swelling, AE may progress to involve the tongue and supraglottic soft tissues, and fatal upper airway obstruction can ensue. Although it is often associated with allergy to foods (ie, nuts or shellfish), stings by insects of the genus Hypenoptera, or administration of other medications (eg, antibiotics), AE is increasingly encountered in patients taking ACEIs. It has been estimated that 0.1% to 0.2% of patients receiving ACEIs develop AE. With more than 40 million people taking these agents in the United States today, this seemingly low incidence of a potentially life-threatening complication is important to clinicians working in emergency departments and ICUs.

The present study has a number of limitations. As with all retrospective studies, the true incidence of the entity being investigated cannot be determined. Cases of AE may have been miscoded or misdiagnosed. The association of AE with ACEI use may have been missed, and patients taking ACEIs may have had AE caused by something else. Clinicians should be cautious in generalizing these findings to other practice settings. For example, the finding that 91% of the patients in this series were African American has uncertain implications, since African Americans comprise 64% of inpatient admissions to the study hospital.

These cautions notwithstanding, this study is important in reminding us of a potentially life-threatening but entirely treatable complication whose frequency is substantial: at Sondhi et al's 600-bed hospital, an average of 9 patients with ACEI-induced AE were admitted each year during the study period. ■

Table

Findings and Interventions among 45 Patients Presenting with ACE-Inhibitor-Related Angioedema

Lip and tongue swelling	45 (100%)	
Pulmonary manifestations	17 (38%)	
	Dyspnea	17/17 (100%)
	Stridor/respiratory failure	5/17 (29%)
	Cough	2/17 (12%)
Dysphagia	9 (20%)	
Drooling	8 (18%)	
Pruritis	6 (13%)	
Admitted to ICU	18 (40%)	
Intubated	5 (11%)	
	ICU pts intubated	5/18 (28%)

Special Feature

Sedation During Mechanical Ventilation

By Leslie A. Hoffman, RN, PhD

Clinicians have been criticized for prescribing too much, as well as too little, sedation for critically ill patients, especially patients who require mechanical ventilation. Over-sedation may prolong weaning from ventilatory support, increase ICU and hospital lengths of stay, and predispose to development of ventilator-associated pneumonia.[1] Inadequate sedation predisposes the patient to pain and discomfort and can evoke a stress response that compromises recovery.[2] Therefore, it is important to strive to achieve the proper balance when administering sedation to mechanically ventilated patients. This essay reviews ways to achieve this balance through bedside assessment, establishing patient oriented sedation goals, using reliable and valid scales to monitor goal achievement, and implementing protocols in ways that are likely to promote clinician acceptance.

Bedside Assessment: Investigate Before Sedating

Agitation is a common problem in ICU patients of all ages. It is also a problem with multiple potential causes. Causes that can lead to devastating problems, if missed, include hypoxemia, hypercarbia, hypoglycemia, visceral pain (eg, myocardial infarction, intestinal ischemia, tension pneumothorax), central nervous system infections, and drug intoxication and withdrawal. Other potential causes include other pain, uncomfortable bed positions, inadequate ventilator flows, fear, and anxiety.[1] When patients are agitated or anxious, the first priority should be to conduct a thorough assessment to identify and treat any underlying physiologic or environmental causes. Non-pharmacologic measures may be appropriate, eg, reassurance, repositioning, and decreased light and noise levels.[3] Withdrawal from alcohol or drugs can be an unrecognized cause of agitation. For this reason, all patients admitted to the ICU should be assessed for signs and symptoms of withdrawal on admission and for several weeks thereafter.[2] Using this approach, sedatives become the end of a chain of thinking rather than the beginning. The complexity of the analysis requires a bedside assessment, rather than the more simple solution of a telephoned order.

Sedation Protocols—The First Key to Consistency

It is important that a sedation goal be established for each patient, regularly reassessed, and changed when indicated.[2] The need for established goals is particularly important in academic institutions and other settings where frequent rotation of covering physicians is the norm. Beyond ensuring comfort, the most compelling goal is to improve ability to tolerate mechanical ventilation.[1] For most patients, the optimum state is lightly asleep, or awake, alert and able to communicate, cooperate and tolerate the care regimen.

When patients are awake and arousable, they are better able to participate in their care and assist health team members in assessing their problems and progress.[1] In a study designed to compare the sedative effects of midazolam and propofol, Kress and colleagues[4] achieved this goal while sedatives were infusing in 60% of patients receiving morphine and midazolam. With a regimen of propofol and morphine, this percentage decreased to 30%. In some instances, heavy sedation is required, eg, during poorly tolerated mechanical ventilation modes such as inverse ratio ventilation and permissive hypercapnia or during neuromuscular blockade.

Treatment goals are most easily accomplished if they are directed by a protocol that identifies target sedation levels, the medications used to achieve these goals, administration route (such as IV bolus vs IV continuous infusion), and adjustments in dosage to maintain target sedation levels.[1,3] In addition to ensuring a uniform approach, protocol-directed sedation has been shown to accomplish other important goals. Brook and colleagues[5] randomly assigned 321 mechanically ventilated patients to receive protocol-directed sedation (n = 162) or non-protocol directed sedation (n = 159). Patients in the protocol-directed group required fewer days of mechanical ventilation and were discharged more quickly from the ICU and hospital. Patients randomized to protocol-driven sedation also had a lower tracheostomy rate, compared to non-protocol patients. Findings of this study are consistent with others that have shown benefits when protocols are used to guide care, eg, weaning from mechanical ventilation. The success of protocols appears to be related, in part, to their ability to facilitate more timely and consistent assessment and speed decision-making. They enable the bedside nurse and respiratory care team to implement care in a more efficient manner.

Regardless of their benefits, protocols may not be enthusiastically accepted. Some have suggested that

change is best facilitated if supported by an "opinion leader." Kaufman and colleagues[6] developed a nurse-driven sedation protocol and tested this premise using three different strategies: 1) daily bedside audit with 24 hour feedback by an ICU physician; 2) weekly audit and feedback by a RN opinion leader; and 3) twice weekly bedside audit with immediate feedback by a RN opinion leader. Use of IV sedatives was not significantly affected by the first 2 strategies. The third strategy substantially decreased overall sedation administration without negatively impacting patient comfort. The findings of this study suggest that protocol success can be enhanced by weekly audits and nursing feedback

Objective Measures of Sedation: The Second Key to Consistency

Sedation scales provide objective validation of subjective impressions regarding sedation goals. An ideal sedation scale should be simple to complete, accurately describe sedation or agitation using clearly defined categories and have documented reliability and validity.[1-3] Of available sedation scales, the Richmond Agitation-Sedation Scale (RASS) appears to best meet these goals.[7,8] The RASS uses a 10-point scale ranging from +4 (combative) to 0 (calm) to -5 (unarousable) based on observation of patient behavior and response to verbal and physical stimulation (*see Table 1*).[1,8] It requires less than 20 seconds to perform[8] and has been shown to be highly reliable when used by nurses and intensivists.

In 38 mechanically ventilated ICU patients, the RASS demonstrated excellent inter-rater reliability among nurses, intensivist physicians, and neuropsychiatric experts.[8] RASS scores also demonstrated the ability to distinguish between levels of consciousness and correctly identified fluctuations within patients over time when comparisons were made between clinician scores and assessment by neurospsychiatric experts. The RASS also demonstrated excellent construct validity when compared with an attention screening examination, Glasgow Coma Scale scores, the quantity of medications administered, and ratings using bispectral electroencephalography (BIS). There was also high acceptance by nursing with 92% of respondents agreeing with the RASS scoring scheme and 81% agreeing that the instrument was effective in guiding goal-directed sedation therapy.[8]

There are several additional scales that have been used for sedation assessment. Although not intended for use as a clinical monitoring tool, the Ramsey Scale has been used extensively to monitor sedation levels in both clinical practice and research studies.[8] This scale categorizes patients into 3 awake states and 3 asleep states, ranging from alert and agitated to asleep and unrespon-

Table 1
The Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very Agitated	Pulls or removes tube(s), or catheter(s); aggressive	
+2	Agitated	Frequent nonpurposeful movement; fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert & Calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (> 10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to voice (< 10 seconds)	
-3	Mod. Sedation	Movement or eye opening to voice (but no eye contact)	
-4	Deep Sedation	No response to voice, but movement or eye opening to physical stimulation	Physical Stimulation
-5	Unarousable	No response to voice or physical stimulation	

Procedure for Using RASS Assessment

1. **Observe patient**
   - Patient is alert, restless, or agitated — Score 0 to +4
2. **If not alert, state the patient's name and say to open eyes and look at speaker**
   - Patient awakens with sustained eye opening and eye contact — Score -1
   - Patient awakens with eye opening and contact, but not sustained — Score -2
   - Patient has any movement in response to voice but no eye contact — Score -3
3. **When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum**
   - Patient has any movement to physical stimulation — Score -4
   - Patient has no response to any stimulation — Score -5

sive. The definitions of the various scores are not very useful, eg, the scale groups mildly anxious, agitated and severely agitated patients into one category. Notably, it has never been objectively validated. The Sedation-Agitation Scale expands the 6-point Ramsey scale by adding one point and more detailed descriptions.[9] It has been shown to have acceptable reliability and validity in critically ill patients. However, it does not provide direction in crossover situations, eg, when patients appear sedated but become agitated once aroused. The Motor Activity Assessment Scale, adapted from the SAS, has also been shown to be reliable and valid when used in critically ill patients.[10] However, it has not been extensively tested.

Strategies for Administering Sedatives: Less is More

In 1998, Kollef and colleagues[11] reported findings of a study that indicated that continuous infusion of sedatives prolonged mechanical ventilation, ICU and hospital lengths of stay when compared with intermittent sedation strategies or no sedation. The study did not use a randomized design, which is a limitation, but did alert clinicians to previously unrecognized complications of continuous sedative infusion. In 2000, Kress and colleagues[12] reported findings from a study in which patients were randomized to receive a daily interruption in sedative infusion, which allowed them to awaken, vs continuous infusions interrupted only at clinician discretion. For intervention patients receiving paralytic drugs, sedative infusions were stopped after administration of the paralytic drug had been stopped. The median duration of mechanical ventilation was significantly less in the group that awakened daily (7.3 vs 4.9 days), as was the median length of stay in the ICU (9.9 vs 6.4 days). In addition, complications (such as removal of the endotracheal tube) occurred less frequently in the daily awakening group. Findings of this study changed practice as they supported daily interruption of sedative infusion as a easy to implement, cost-effective intervention that could improve patient outcomes. Daily awakening has the additional advantage of allowing a daily neurologic examination and reevaluation of sedation needs.

While daily awakening may have short-term advantages, there were concerns regarding adverse psychological reactions. However in a follow-up study, Kress and colleagues[13] reported fewer, rather than more, problems in the intervention group. None of the patients in the intervention group recalled awakening, despite daily attempts to awaken them. There were fewer signs of post-traumatic stress disorder in the intervention group and a lower incidence of chronic anxiety. The intervention group also had lower depression scores. Thus, in contrast to the initial perceptions of many, patients in the group that underwent daily awakenings fared significantly better than control patients on all measured variables.

Summary

Available evidence indicates that it is less important what drugs are administered than that they are properly titrated to optimize patient comfort and minimize complications using goal-directed therapy. Key components include a thorough bedside assessment when patient response indicates, goal-directed sedation, use of protocols, and objective assessment of sedation levels using validated, reliable instruments. ■

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CME Questions

10. Which of the following has been suggested as a barrier to implementation of unrestricted visiting hours?

a. Family visits increase physiologic stress for patients
b. Visitors at the bedside impede the delivery of care
c. Prolonged visitation can lead to exhaustion in the visitor
d. All of the above
e. None of the above

11. Mortality among patients with advanced cirrhosis who required ICU admission and invasive mechanical ventilation was most strongly correlated with:

a. severity of liver disease.
b. APACHE II score.
c. SAPS score.
d. ICU resource use.

12. Mechanisms that may help keep families informed about patients' conditions to allow them to feel comfortable away from the hospital include:

a. beepers for the family to be contacted if there is a change in the patients' condition.
b. an automated secure phone message updated with changes in the patients' condition.
c. a regularly scheduled update from the managing physician.
d. All of the above
e. None of the above

13. In the study of adverse events related to intra-hospital transportation of critically ill patients, significant adverse outcomes occurred in what proportion of incidents?

a. 11%
b. 21%
c. 31%
d. 51%
e. 71%

14. Which of the following are potential problems with the study describing adverse patient incidents associated with transportation to other parts of the hospital?

a. It probably underestimates the true incidence of such problems
b. Reporting was voluntary
c. Reporting was anonymous
d. The accuracy of the reports cannot be verified.
e. All of the above

15. In the retrospective series of patients with angiotensin-converting enzyme inhibitor-induced angioedema, mortality among patients requiring ICU admission was:

a. 0%.
b. 10%.
c. 20%.
d. 30%.
e. 40%.

Answers: 10 (d); 11 (a); 12 (d); 13 (c); 14 (e); 15 (a)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

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a. Total No. Copies *(Net Press Run)*			933	920
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	666	663
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	3	3
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	22	20
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c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			715	708
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	15	16
	(2)	In-County as Stated on Form 3541	1	1
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			25	25
f. Total Free Distribution *(Sum of 15d and 15e)*			41	42
g. Total Distribution *(Sum of 15c and 15f)*			756	750
h. Copies Not Distributed			177	170
i. Total *(Sum of 15g, and h.*			933	920
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			95	94

16. Publication of Statement of Ownership — Publication required. Will be printed in the November 2004 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/27/04

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

In Future Issues:

Significance of Brain-Type Natiuretic Peptide in Critical Illness

PHARMACOLOGY WATCH

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

The FDA and Merck Fielding Concerns About Vioxx

Merck announced on September 30th that it is voluntarily withdrawing rofecoxib (Vioxx) from the worldwide market. The decision was based on data from the APPROVe (Addenomatous Polyp Prevention on Vioxx) trial, a company sponsored perspective randomized, placebo-controlled trial designed to assess whether the drug reduces the risk of colorectal polyps in patients with a history of colorectal adenomas. However, after 18 months of the study, patients on 25 mg of rofecoxib were noted to have an increased risk of cardiovascular events such as myocardial infarction and stroke, compared to those patients taking placebo. The FDA supported Merck's action and acknowledged that, while the risk to any individual on rofecoxib is small, the risk increases with continued use. The APPROVe trial showed that the risk of cardiovascular events with rofecoxib was twice that of placebo, according to information published on the FDA News website (fda.gov/bbs/topics/news/2004/NEW01122.html). Previous studies, including a recently reported Kaiser Permanente/FDA retrospective trial, showed the risk to be 3 times that of placebo. The FDA is investigating whether cardiovascular risk may be a class effect of COX-2 inhibitors (coxibs), and is reviewing data from similar trials with celecoxib (Celebrex) and valdecoxib (Bextra). Meanwhile, Merck is initiating a buy-back program for unused Vioxx prescriptions, reimbursing patients for their unused prescriptions. The withdrawal has enormous implications for the company and its shareholders, not only from the loss of nearly $2 billion in revenues from drug, but lost share value for the company stock and the risk of future legal action. It is estimated that 2 million patients in the United States were taking Vioxx at the time of the withdrawal, and over 84 million people worldwide have taken drug at some point since its approval in May 1999. The October issue of the *New England Journal of Medicine* has 2 scathing reviews of Merck and the FDA with regard to the approval and marketing of rofecoxib. Dr. Eric Topol of The Cleveland Clinic, who was one of the first to raise concerned about rofecoxib, calls for a full Congressional review of this case. The senior executives at Merck, and the leadership of the FDA, share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health (*N Engl J Med.* 2004;351:1707-1709). Dr. Garrett FitzGerald of the University of Pennsylvania suggests evidence has been there all along that coxibs, including celecoxib and valdecoxib, may promote cardiovascular disease by blocking prostaglandin I2, which inhibits platelet aggregation, promotes vasodilation, and prevents the proliferation of vascular smooth muscle cells in vitro. At the same time, coxibs have little effect on thromboxane A2, which is responsible for platelet aggregation.

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Traditional NSAIDs and aspirin block thromboxane production, accounting for their cardioprotective effects. Dr. FitzGerald states, "It is essential to determine whether cardiovascular risk is or is not a class effect." The burden of proof now rests with those who claim that this is a problem for rofecoxib alone, and does not extend to other coxibs." (*N Engl J Med*. 2004;351:1709-1711).

Erythromycin and the Risk of Sudden Death

Erythromycin may be associated with an increased risk of sudden death, according to new study in the *New England Journal of Medicine*. Oral erythromycin, which is extensively metabolized by cytochrome P-450 3A (CYP3A), prolongs cardiac repolarization, and has been associated with reports of torsades de pointes. Commonly used medications that inhibit CYP3A may increase plasma erythromycin levels, increasing the risk of ventricular arrhythmias and sudden death. Researchers from Vanderbilt reviewed data from a Tennessee Medicaid cohort that included more than 1.2 million person-years of follow-up and 1476 confirmed cases of sudden death from cardiac causes. The patients in the study were relatively young, with a mean age of 45. Seventy percent were female, and 58% were white. The multivariate adjusted rate of sudden death from cardiac causes among patients using erythromycin was twice as high as that among those who had not used any of the study antibiotic medications (incident-rate ratio 2.01; 95% CI, 1.08-3.75; $P = 0.03$). There was no increase in sudden death among patients using amoxicillin, or former users of erythromycin. For patients who were taking erythromycin with concurrent use of a CYP3A inhibitor (nitroimadazole antifungal agent, diltiazem, verapamil, or troleandomycin), the adjusted rate of sudden death was 5 times as high (incident rate ratio 5.35; 95% CI, 1.72-16.64; $P = 0.004$). The authors conclude that erythromycin should be avoided in patients who are taking CYP3A inhibitors (*N Engl J Med.* 2004;351:1089-1096).

Vaccine Shortage Putting Americans At Risk

Just as healthcare providers are about to start their annual flu vaccination program, British regulators have shut down Chiron Corporation's Liverpool flu vaccine manufacturing plant due to sterility problems. Chiron was expected to supply nearly 50 million doses of vaccine this year, half of the hundred million doses health officials expected to be administered to Americans this fall. Aventis, the other major supplier of vaccine, has told health officials that he could produce an additional million doses this year, but no more. Compounding the shortage, is the addition of 2 groups of patients recommended to receive the vaccine this year—children between the ages of 6 and 23 months (who require 2 doses 1 month apart) and pregnant women (or women who anticipate being pregnant during the flu season). Other high-risk patients include people over age 65, people in nursing homes, people with chronic illnesses, and those caring for people in these groups. Healthcare workers are also considered the highest priority for vaccination. The nasal flu vaccine, FluMist, does little to alleviate the shortage since it is only indicated for healthy children and adults between the ages of 5 and 49 years.

FDA Actions

The FDA will move ahead with warnings for many antidepressants stating that the drugs sometimes raise the risk of suicidal behavior in youth. The recommendation comes after an agency advisory panel, on a split vote, recommended a Black box warning. The agency may not go that far, however, since some advisors were concerned that warnings may discourage treatment of depressed children and teens who can benefit from antidepressants medications. The drugs subject to the warning are those with the brand names Prozac, Paxil, Wellbutrin, Zoloft, Celexa, Effexor, Luvox, and Remeron.

The recently approved antidepressant duloxetine (Cymbalta) has received FDA approval for treatment of pain associated with diabetic neuropathy. This is the first drug approved for this indication in this country. In 2 studies submitted to the FDA, the drug reduced 24-hour average pain levels, compared with placebo, in patients who had diabetes for an average of 11 years, and had neuropathic pain for average of 4 years.

The FDA has approved a new extended release formulation of hydromorphone for the management of persistent moderate-to-severe pain in patients requiring continuous, round-the-clock opioid pain relief for extended periods of time. The product is an extended release formulation that can be dosed once a day, and will be available in 12, 16, 24, and 32 mg capsules. The drug is only recommended for patients already receiving opioid therapy who have demonstrated opioid tolerance, and who require a minimum total daily opioid dose equivalent to 12 mg of oral hydromorphone. It will be marketed by Purdue pharmaceuticals with the trade name Palladone.