CRITICAL CARE ALERT®

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

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INSIDE

Index and CME evaluation enclosed with this issue

Financial Disclosure:
Critical Care Alert's Editor, David J. Pierson, MD, nurse planner Leslie A. Hoffman, PhD, RN, and peer reviewer William Thompson report no financial relationships related to this field of study.

Intensive Insulin Therapy in the Medical ICU

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *The use of an insulin infusion protocol to keep blood glucose between 80 and 110 mg/dL in adult medical ICU patients had no overall effect on mortality but appeared to decrease selected complications. Survival was improved by tight glucose control among patients remaining in the ICU beyond 3 days.*

Source: Van den Berghe G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354:449-461.

IN A PREVIOUS STUDY INVOLVING PATIENTS IN A SURGICAL ICU[1], Van den Berghe and associates at the Catholic University of Leuven, Belgium, showed that tight control of serum glucose levels by means of a strict insulin infusion protocol decreased both morbidity and mortality. In the present study, these same investigators sought to determine whether the same results would be found in medical ICU patients, who tended to have greater severity of illness, more co-morbidities, and higher mortality rates. In a prospective, controlled clinical trial, the authors randomized medical ICU patients who were predicted to require at least 3 days of ICU care to either conventional therapy with respect to serum glucose or a tight-control protocol to keep values between 80 and 110 mg/dL. Patients randomized to receive conventional therapy were administered insulin when blood glucose exceeded 215 mg/dL, but the infusion was tapered when levels fell below 180 mg/dL.

Of 2110 adult medical ICU patients screened during a 3-year period, 1200 were randomized to conventional vs tight-control glucose management. Also, 767 of these patients remained in the ICU for at least 3 days. Among all 1200 patients in the study (intention-to-treat analysis), in-hospital mortality was 40% in the conventional-treatment group vs 37% in the intensive-treatment group, a non-significant difference ($P = 0.33$). However, among the patients who remained in the ICU for at least 3 days, there was a significantly lower in-hospital mortality among those who received the tight-glucose-control therapy (52% vs 43%; $P = 0.009$). Morbidity, in the

form of newly acquired renal dysfunction, delayed weaning from ventilatory support, and prolongation of ICU stay, was less with the intensive-therapy regimen, both in the overall group and in those patients staying in the ICU for at least 3 days.

COMMENTARY

In this large clinical trial conducted in the medical ICU of a single institution, the use of an intensive insulin therapy protocol to keep blood glucose levels between 80 and 110 mg/dL had no effect on overall mortality. The fact that mortality was significantly reduced among the 64% of patients who remained at least 3 days in the ICU (the investigators' target population) means that mortality had to be correspondingly increased among patients who spent less time in the ICU. This was apparently the case, a finding for which the authors offered no ready explanation. That the investigators were unable to predict in advance which patients would remain in the ICU at least 3 days—and thus, which patients would presumably be helped rather than harmed by intensive insulin therapy—makes potential application of the study's findings problematic for the clinician.

The introduction, investigation, and adoption of new ICU therapies often seem to follow a distinct sequence. An initial study—usually relatively small and from a single center—is published showing markedly positive results from the new treatment. In a number of such initial studies, mortality rates in the control population—patients receiving standard care rather than the new treatment—have been unusually high. Often, aspects of patient selection, potentially confounding conditions and therapies, and other factors have raised questions about the study and about the generalizability of its findings. These cautions notwithstanding, the new therapy tends to be widely embraced by intensivists, sometimes even to the point of becoming a standard of care. Subsequently, larger, multi-center studies are published. Sometimes these more extensive investigations confirm the effects of the new therapy and validate the findings of the initial paper. This was the case with lung-protective ventilation for acute lung injury and ARDS, and also for noninvasive ventilation for acute hypercapnic respiratory failure in patients with COPD. However, in numerous other instances the larger-scale trials have failed to demonstrate the benefit found in the initial study. Therapies such as late corticosteroids and inhaled nitric oxide for ARDS, and supra-physiologic oxygen-delivery goals for severe shock come to mind here, among others.

What will the "bottom line" prove to be with respect to intensive insulin therapy when the more extensive studies called for by Van den Berghe et al are done? Such studies are reportedly underway at the present time.[2] How should the clinician manage blood glucose levels in critically ill patients, based on current information? In an editorial accompanying the paper by Van den Berghe and colleagues, Malhotra[3] lists 3 possible courses of action. One would be to go along with current trends and simply adopt the "tight glucose control" approach, on the rationale that it seems to benefit some patients and its adverse effects do not seem to be too severe. This approach has already become a standard of care in many ICUs around the world, and is included in the most recent guidelines for the management of sepsis.[4] Another approach would be to withhold intensive insulin therapy until its evidence base is more complete and more confident conclusions about when and how to use it can be drawn. A reasonable case could be made for either of these approaches.

Malhotra suggests a third, more middle-of-the-road approach.[3] During the first 3 days in the ICU, try to keep blood glucose levels below 150 mg/dL. If critical illness continues and the patient remains in the ICU beyond 3 days, consider tighter glucose control to blood levels between 80 and 110 mg/dL, as employed by Van den Berghe et al. While the effects of tight glucose con-

Critical Care Alert, ISSN 1067-9502, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Critical Care Alert,* P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issues date.

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Customer Service: 1-800-688-2421

Customer Service E-Mail Address: customerservice@ahcpub.com

Editorial E-Mail Address: robert.kimball@thomson.com

World Wide Web: http://www.ahcpub.com

Subscription Prices

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1 year *with* free AMA Category 1 credits: $289

(Student/Resident rate: $120)

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Questions & Comments

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trol starting at ICU day 3 have not specifically been investigated, this approach seems reasonable, and would be supported by the current study as well as other currently available data. ■

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Intensivist-to-Bed Ratio Impacts Length-of-Stay in the Medical ICU

ABSTRACT & COMMENTARY

By Leslie Hoffman, PhD, RN

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

Synopsis: *Differences in intensivist-to-bed ratio ranging from 1:7.5 to 1:15 were associated with an increased ICU length-of-stay.*

Source: Dara SI, et al. Intensivist-to-bed ratio: association with outcomes in the medical ICU. *Chest*. 2005; 128:567-572.

THIS STUDY EXAMINED THE EFFECT OF VARIATIONS IN ICU staffing, defined in terms of intensivist-to-ICU bed ratio, on ICU length-of-stay (LOS) and ICU and hospital mortality. The study was conducted at the Mayo Clinic in Rochester, MN over a 9-month period when the medical ICU underwent a series of planned changes which resulted in its capacity increasing from 15 to 24 beds. As a consequence of these changes, the intensivist-to-bed ratio varied from 1:15 (initial ratio) to 1:7.5, 1:9.5, and 1:12 (final ratio), yielding 4 periods of comparison. Other than the change in bed ratio, the role of the intensivists did not undergo any major change. The intensivists were responsible for the delivery of all care in the ICU, made rounds at least twice daily, supervised all invasive procedures, wrote daily progress notes, and supervised educational activities of the critical care fellows and first and third year internal medicine residents who rotated through the unit. During the study period, there were no changes in the nurse-to-patient ratio (1:1 or 1:2) or frequency of house staff rotation (4-5 weeks).

A total of 2,492 patients were admitted to the medical ICU during the 9-month study interval. There were no statistically significant differences in severity of illness (APACHE III scores), predicted mortality rate after case-mix adjustment, or ICU readmission during the 4 periods of comparison. Also, there were no statistically significant differences in the ICU admission source (predominately the Emergency Department) during the 4 periods.

The ICU period with a 1:15 intensivist-to-bed ratio had a longer adjusted ICU LOS compared to the period with a 1:75 ($P < .0001$), 1:9.5 ($P = .0003$), and 1:12 ratio ($P < .0001$). The difference was not significant when comparisons were made between periods with a 1:75 bed ratio vs 1:9.5 ($P = .20$) or 1:12 ($P = .51$) ratio. Differences in bed ratio were not associated with significant differences in ICU or hospital mortality or hospital LOS.

COMMENTARY

In this study, there were no statistically significant differences in severity of illness during the 4 time periods, suggesting that changes in the number of available ICU beds did not influence the threshold for admission to the medical ICU. Also, there was no change in ICU or hospital mortality after case-mix adjustment, suggesting that variations in intensivist-to-bed ratio did not influence patient survival. However, there was an increase in ICU, but not hospital, LOS. This suggests that patients were stabilized and transferred from the medical ICU more quickly during periods when the intensivist-to-bed ratio was 1:7.5 compared to 1:15.

As noted by Alan Morris,[1] humans are limited in their ability to simultaneously analyze large quantities of information, a concern given the thousands of pieces of information analyzed by ICU clinicians each day. By one estimate, an intensivist may be confronted with 1,000 pieces of information on each patient each day. In addition, as the number of patients managed increases,

contact is more intermittent, increasing the likelihood that changes in the management plan will not occur as quickly.

In ICUs, the nurse-patient ratio is commonly varied from 1:1 to 1:2 dependent on patient needs. In contrast, the number of intensivists is usually determined by the size of the ICU and does not fluctuate dependent on changes in patient acuity or increased needs for teaching, supervision and consultation due to rotation of house staff. Findings of this study should be of interest to policy makers as they consider the projected increase in demand for critical care service. Although no differences were seen in mortality or hospital LOS, changes in ICU LOS can translate into substantial cost savings. The ability to focus on fewer patients has a number of additional advantages, including improved family and patient satisfaction, better end-of-life care, and improved interdisciplinary coordination. ■

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Patients' Recollections of Therapeutic Paralysis in the ICU

ABSTRACT & COMMENTARY

By Karen L. Johnson, RN, PhD

Assistant Professor, School of Nursing, University of Maryland

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

Synopsis: *Patients who have neuromuscular blocking agents in the ICU often recall the experience, and frequently report a common group of recollections.*

Source: Ballard N, et al. Patients' recollections of therapeutic paralysis in the intensive care unit. *Am J Crit Care*. 2006;15:86-94.

Ballard and colleagues conducted this qualitative study to obtain recollections of critically ill patients who were given neuromuscular blocking agents (NMBAs) (for a minimum of 6 hours) and sedatives and/or analgesics. Patients were interviewed 48-72 hours after extubation. They were asked to describe what they remembered about the time when they were on the ventilator and unable to move, and what events or conversations they remembered. Eleven patients (7 women, 4 men) were interviewed. The mean age was 43 years (range, 19-69 years). Most patients had a diagnosis of respiratory failure (5) and the rest had various medical conditions (COPD, overdose).

Four themes emerged from the data: 1) back and forth between reality and the unreal, between life and death; 2) loss of control, especially when being restrained; 3) fear of almost dying; and 4) a sense of being cared for. Results from this study provide additional evidence that patients can remember having both positive and negative experiences during therapeutic paralysis.

■ COMMENTARY

This study is a replication of a study we conducted 7 years ago.[1] Our study was conducted with 12 patients in a trauma ICU and this study was conducted with 11 patients in a medical ICU. The results of both studies are strikingly similar: patients do recall events and experiences—both positive and negative—during therapeutic paralysis.

Patients in both studies could not distinguish reality from dreams. They reported they could not figure out where they are. One patient in the current study thought she left the hospital, got lost, knew she was sick, but could not find her way back to the hospital. One patient in our study dreamed she was on a roller coaster and couldn't get off (actually she was on a kinetic therapy bed). The fact that patients don't know where they are should be of concern to nurses. Nurses are supposed to do frequent reality orientation with ICU patients. Compliance with this intervention is probably sporadic.

This also raises the question of the adequacy of sedation. Patients in this study all received sedation (lorazepam, midazolam, or propofol), but the mean dose or method used to evaluate the level of sedation was not reported. Clinical practice guidelines[2] call for adequate sedation with administration of NMBAs, in accordance with clinical judgment. However, it is difficult to assess sedation levels in these patients. Recently the American Association of Critical Care Nurses proposed a Sedation Assessment Scale,[3] but clinical trials to determine its reliability and validity have not been done. The Bispectral Index (BIS), calculated from EEG data, was designed to measure the depth of hypnosis during sedation.[4,5] BIS does correlate with the Ramsay Scale.[6,7] However associations among the BIS and other sedation scales vary among medical, surgical, and trauma patients.[8-11]

Fortunately, patients in this study, as in our study,

could not recall painful procedures or experiences while under therapeutic paralysis. However, in the current study 4 of the 11 patients did not receive analgesics while undergoing therapeutic paralysis! Most of us would agree with others[12] who believe that the use of NMBAs in patients who have not received analgesics is ethically and therapeutically contraindicated.

Patients in this study had a sense of being out of control, especially when being tied down. Why are patients who receive NMBA—to induce paralysis of voluntary muscle activity—being restrained? Despite the fear of dying and loss of control, the patients in this study had a sense of being cared for. As in our study, patients recalled a sense of emotional support and encouragement from their nurses and family members.

This study provides additional evidence that patients recall experiences during therapeutic paralysis. Extensive research has been done on the experience of awareness during general anesthesia. JCAHO published a Sentinel Event Alert on awareness during anesthesia.[13] JCAHO now recommends education of staff about awareness during anesthesia, effective anesthesia monitoring techniques, follow up of all patients who have experiences of awareness during anesthesia, and counseling for those who experience post-traumatic stress disorder.

Unfortunately, the subject of recollections and awareness of patients during therapeutic paralysis in the ICU has not garnered the same degree of scrutiny as awareness during general anesthesia in the OR. Fortunately the number of patients receiving therapeutic paralysis in the ICU is now relatively small as compared to when our study was done. However, we do need to evaluate how well we are managing pain and sedation in patients who receive therapeutic paralysis. Quality improvement programs should be instituted to assess for awareness during therapeutic paralysis and to provide follow-up and referral as needed. ■

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Special Feature

Care Bundles in the ICU

By James E. McFeely, MD

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

THE INSTITUTE OF MEDICINE HAS DOCUMENTED THAT the hospital—and the ICU in particular—is an environment in which errors are all too frequent.[1,2] The work environment in the ICU can be chaotic, and we are all familiar with the many distractions that are present as we attempt to write orders to implement a plan of care for any particular patient. Monitors alarm, pagers go off, and other caregivers frequently interrupt your train

of thought with questions that may or may not be related to the patient on whom you are trying to focus. These variables, as well as the simple fact of human fallibility, result in decreased reliability and chaotic decision-making in the ICU.

All intensivists like to think that they do well at implementing what they consider to be the best practice for their patients. Despite our best efforts, however, it is well documented that we fail to do so on a daily basis. The literature is replete with examples such as the failure of best institutions to implement low-tidal-volume ventilation in patients with the acute respiratory distress syndrome (ARDS) up to 30-40% of the time,[3] or the well-documented failure rate for implementation of management guidelines for treatment of congestive heart failure.[4] In a prospective study of implementation of a bundle for management of sepsis, there was only a 52% compliance with all elements, even in a research setting.[5]

It is not that physicians think these interventions are inappropriate for any given number of patients; rather, the high failure rates reflect the unreliability of the systems currently in place for implementation. Indeed, in this respect every institution has room for improvement.[6] Those institutions that think they have 100% compliance with any given care plan would be advised to measure their compliance. In almost all cases you'll find yourself falling short of the mark unless you have a multifaceted systematic approach to optimize implementation.

It is well known from the manufacturing industry that scripting work processes stabilizes the system and improves both reliability and reproducibility. In health care, use of care bundles performs a similar function. Bundles are combinations of several interventions that are scientifically demonstrated to improve outcomes in a given disease state. When executed as a group the interventions produce better outcomes than when implemented individually or on an ad hoc basis. In sepsis, for example, implementation of a bundle for the first 6 hours of care resulted in a reduction in mortality from 49% of 23%.[5] The various elements of any given bundle derive from evidence-based medicine, and are included only if they are generally accepted as best practice for a given disease state. When properly implemented, bundles take advantage of the best advancements in medicine as well as in organizational science.

Arguments against the use of bundles focus on the fact that unlike manufacturing processes, which can be readily standardized, treating human illness requires integration of unique data sets for each patient. Indeed, some argue that the use of bundles of care or order sets can result in "cookbook" medicine and might inhibit the individualization of care that may be appropriate in a particular case. Further, the typical intensivist is not the sort that likes to be constrained by fixed order sets.

On the other hand, while it is certainly true that diseases do not necessarily follow the same path in every given patient, for many illnesses—such as sepsis, ventilator-associated pneumonia, and acute myocardial infarction—there are elements of care that can generally be agreed upon as appropriate for almost all patients. The idea, therefore, is not to replace physician expertise with fixed instructions, but to use standardized protocols or bundles as ever-present prompts for each supported intervention in order to minimize human error. By combining the use of bundles of care with the individual expertise of an experienced clinician, you can improve patient care by using the strengths of both. Those institutions that have the best outcomes tend to be the ones using care bundles to optimize their implementation.

In developing and implementing care bundles, only well-accepted, validated interventions should be included. As a rule of thumb, if you can't cite "the reference"—for example, "Rivers's Early Goal Directed Therapy,"[7] or the "ARDSNet Ventilation Strategy"[8]—it doesn't belong in the bundle. A care bundle is no place for the latest fad that's unsupported by the medical literature. Bundles are best kept succinct with clearly defined elements that can be understood by all members of the care team. Moreover, recognizing that diseases do not necessarily follow the same path in every patient, the same level of vigilance needs to remain once bundles are implemented, to be sure that they are appropriately used as part of any given patient's care plan.

Implementation of bundles is a multi-step process:[9]

1. Obtain agreement on what should be included in a given bundle as supported by the medical literature.
2. Measure current performance with each element of the bundle in your institution.
3. Collaboratively develop implementation tools (eg, order sets; checklists) that are appropriate for each hospital's practice environment and obtain buy-in from all relevant stakeholders.
4. Begin to use the tools that have been developed and adjust as necessary in the real world environment.
5. Reassess performance in all measured indicators and adjust appropriately.

Simpler implementation tools are better. Order sets that are too long or present too many choices are unwieldy, increase the risk of error, and decrease the reliability of the end product. Time spent keeping the protocol brief and clear is time well spent.

Table 1

Prevention of Ventilator Associated Pneumonia[10]

- Elevation of the head of the bed > 30 degrees
- Deep Vein Thrombosis Prophylaxis
- Peptic Ulcer Prophylaxis
- Daily Sedation Vacation
- Daily Weaning Assessment

Table 2

Sepsis Acute Resuscitation (first 6 hrs)[11]

Obtain cultures prior to administration of antibiotics
Administer antibiotics within 3 hrs of ED arrival (or within 1 hr for non-ED ICU admissions)
Measure serum lactate
If hypotension is present or lactate is > 4 mmoL/L:

- initial minimum fluid resuscitation of 20 mL/kg (crystalloid or colloid)
- vasopressors for hypotension not responding to fluids: maintain mean arterial pressure ≥ 65 mm Hg

If hypotension persists or lactate is > 4 mmoL/L:

- achieve CVP of ≥ 8 mm Hg
- achieve central venous oxygen saturation ≥ 70%, or mixed venous oxygen saturation ≥ 65%

Table 3

Sepsis Resuscitation within first 24 hrs[11,12]

Administer low-dose corticosteroids
Consider administration of drotrecogin alfa (activated) if appropriate
Maintain tight glycemic control (serum glucose < 150 mg/dL)
Maintain inspiratory plateau pressures 30 cm H_2O or less (ventilated patients)

Table 4

Management of Acute Myocardial Infarction[13]

Aspirin
Beta Blockers
ACE Inhibitors
Lipid-lowering therapy
Smoking cessation
For Acute ST-elevation MI
Door to Drug time < 30 min
Door to Balloon time < 90 min

Table 5

Congestive Heart Failure[14-16]

Assess need for diuretics
ACE Inhibitors
Nonselective beta blockers
Lipid therapy
Smoking cessation
Dietary counseling
Cardiac rehabilitation/exercise program
Aldactone

There are several currently recommended bundles appropriate to the ICU that have been promoted by various societies. In the attached tables you'll see bundles for treatment of sepsis, prevention of ventilator-associated pneumonia, management of acute myocardial infarction, and management of acute congestive heart failure. These are all well established with excellent support in the medical literature and would be excellent choices to begin improving the reliability of care within your ICU. ■

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CME Questions

19. The study by Van den Berghe et al of intensive insulin therapy in medical ICU patients used what target for blood glucose levels in the experimental group?
a. 60-100 mg/dL
b. 80-110 mg/dL
c. 100-150 mg/dL
d. below 150 mg/dL
e. below 215 mg/dL

20. Intensive insulin therapy for tight control of serum glucose levels has been shown to reduce overall mortality in what patient population(s)?
a. Patients in the surgical ICU
b. All patients in the medical ICU
c. Patients remaining in the medical ICU for less than 3 days
d. All patients in both medical and surgical ICUs
d. Patients in the surgical ICU, and patients remaining in the medical ICU for less than 3 days

21. Among patients remaining in the medical ICU for more than 3 days, intensive insulin therapy had which of the following effects?
a. Reduced mortality
b. Reduced incidence of new renal abnormalities
c. Shortened duration of weaning from mechanical ventilation
d. All of the above
e. None of the above

22. Compared to a bed ratio of 1:7.5, an intensivist-to-bed ratio of 1:15 was associated with significantly:
a. higher ICU patient mortality.
b. higher hospital mortality.
c. more ICU readmissions within 72 hours.
d. more adverse events associated with hand offs.
e. longer ICU length-of-stay.

23. Recollections of critically ill patients during therapeutic paralysis can be categorized into which of the following themes?
a. Back and forth between reality and the unreal
b. Loss of control
c. Feeling cared for
d. All of the above
e. None of the above

24. Patients who receive neuromuscular blockade in the intensive care unit should also receive:
a. analgesia
b. sedatives
c. antibiotics
d. All of the above
e. a and b

Answers: 19 (b); 20 (a); 21 (d); 22 (e); 23 (d); 24 (e)

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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Treating Opioid-Dependent Patients with OAT

A Perspective article in the Jan. 17 *Annals of Internal Medicine* reviews pain management in patients with a history of opioid addiction who are receiving opioid agonist therapy (OAT) with maintenance methadone or buprenorphine. These patients present unique challenges that frequently result in suboptimal treatment of acute pain.

The authors provide an excellent review of these challenging patients and point our 4 common misconceptions: 1) Maintenance opioids provide analgesia—not only is this not the case, but OAT may reduce the effectiveness of standard pain relief measures; 2) Opioids for analgesia may result in addiction relapse—there is no evidence that treatment of acute pain triggers relapse; 3) The additive effects of opioid analgesics and OAT may cause respiratory and CNS depression—tolerance to the respiratory and CNS effects of opioids develops rapidly and is not exacerbated by acute therapy; 4) Reporting pain is drug-seeking behavior—as long as there is clinical evidence of pain, or an acute injury, pain may be safely treated. Drug seeking and manipulation is more likely characterized by vague reports of long-term pain than requests for short term pain relief. Plus, patients on OAT are less likely to experience euphoria associated with coadministered opioids, so there is less incentive to drug seek.

The authors provide specific pain treatment recommendations for patients on methadone and buprenorphine. They conclude, "Addiction elicits neurophysiologic, behavioral, and social responses that worsen the pain experience and complicate provision of adequate analgesia. These complexities are heightened for patients with opioid dependency who are receiving OAT, for whom the neural responses of tolerance or hyperalgesia may alter the pain experience. As a consequence, opioid analgesics are less effective; higher doses administered at shortened intervals are required. Opioid agonist therapy provides little, if any, analgesia for acute pain. Fears that opioid analgesia will cause addiction relapse or respiratory and CNS depression are unfounded. Furthermore, clinicians should not allow concerns about being manipulated to cloud good clinical assessment or judgment about the patient's need for pain medications. Reassurance regarding uninterrupted OAT and aggressive pain management will mitigate anxiety and facilitate successful treatment of pain in patients receiving OAT" (Alford DP, et al. *Ann Intern Med*. 2006;144:127-134).

Long-Term Effects of Warfarin Use

Warfarin use may be associated with osteoporosis and fractures in men, but not women, with atrial fibrillation, according to new study. In a retrospective cohort study of Medicare benefici-

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aries with atrial fibrillation in United States, 4461 patients on long-term warfarin therapy were compared to 7587 patients who were not prescribed warfarin. The adjusted odds ratio of fracture was 1.25 in patients who took warfarin (95% CI, 1.06-1.48). The odds ratio for men was 1.63, and a nonsignificant 1.05 for women. In patients who were prescribed warfarin for less than one year, the risk of osteoporotic fracture was not increased significantly. The authors speculate that since warfarin blocks vitamin K dependent clotting factors, it may also block vitamin K dependent osteocalcin and other bone matrix proteins. Interestingly, use of beta blockers reduced the risk of fracture in this population. The authors conclude that long-term use of warfarin was associated with osteoporotic fractures in men with atrial fibrillation, and that beta-blockers may be somewhat protective (Gage BF, et al. *Arch Intern Med*. 2006;166:241-246).

Statins' Multiple Benefits

Mounting evidence suggest that statins have benefits beyond their ability to lower LDL cholesterol. Multiple studies show that statins reduce inflammation in patients without heart failure. Now, 2 new studies suggest that they also reduce inflammation in patients with heart failure. In a study from Emory University, 108 patients with nonischemic heart failure were randomized to atorvastatin 20 mg per day or placebo. Inflammatory markers such as C reactive protein, interleukin-6, and TNF-alpha were all reduced in the atorvastatin group. Atorvastatin treated patients also showed an improvement in LVEF from 0.33-0.37 over one year (P = 0.01) (Sola S, et al. *J Am Coll Cardiol*. 2006;47:332-337).

A second study, from Harvard, in patients with heart failure showed that atorvastatin 10 mg/ day led to an 8% reduction in TNF receptor 1, a 37% reduction in C reactive protein, and a 17% reduction in endothelin-1 (Mozaffarian D, et al. *Am J Cardiol*. 2005;96:1699-1704). Atorvastatin may also have anti-thrombotic effects in patients with unstable angina according to a study from Greece. Forty-five patients with normal cholesterol levels and unstable angina were randomized to 10 mg of atorvastatin or placebo, starting right after hospital admission and continuing for 6 weeks. After one week of treatment circulating levels of anti-thrombin III, factor V, and von Willebrand factor were all significantly reduced in the atorvastatin group (Tousoulis D, et al. *Int J Cardiol*. 2006;106:333-337).

FDA Actions

The FDA has approved the first inhaled insulin for the treatment of adults with type I and type 2 diabetes. Inhaled insulin, a powder form of recombinant human insulin, has been in development for over 10 years, and has been the subject of intense scrutiny by the FDA. Concerns over long-term safety, particularly in people with underlying lung disease, has delayed approval, and safety in children and teenagers is still under investigation. Inhaled insulin is delivered through a device that is significantly larger than an asthma inhaler and, even folded, is the size of a flashlight. A blister pack of insulin powder is inserted into the device, which is then triggered. It is not to be used by smokers or people who quit smoking within last 6 months, and is not recommended for people with asthma, bronchitis, or emphysema. The FDA also recommends pulmonary function testing prior to starting inhalation therapy, and every 6 to 12 months thereafter. Although the product is approved for treatment of both type I and type 2 diabetes, fewer than 30% of type I diabetics achieve adequate control with inhaled insulin alone. Inhaled insulin is a joint effort by Pfizer, Sanofi-Aventis, and Nektar Therapeutics. It will be marketed under the trade name Exubera.

The FDA has approved an intravenous form of Ibandronate that can be administered every 3 months for the treatment of postmenopausal osteoporosis. The 3 mg dose is injected intravenously over 15 to 30 seconds by a healthcare professional. The drug is an option for women who cannot take pills or are unable to sit upright for 30 to 60 minutes after taking an oral bisphosphonate. Efficacy with the injectable form of ibandronate was better than once-a-day oral dosing of Ibandronate 2.5 mg in a study of over 1300 women with osteoporosis. Intravenous and oral forms of the drug were equally well tolerated. The FDA is recommending measurement of serum creatinines prior to administration each dose. Ibandronate is also approved is a 2.5 mg once a day oral dose and a 150 mg monthly oral dose. All 3 formulations are marketed as Boniva.

Berlex's combination estradiol-levonorgestrel patch (Climara Pro) has been approved for the indication for prevention of postmenopausal osteoporosis in women with an intact uterus. The patch was previously approved for the indication of moderate to severe vasomotor symptoms associated with menopause. The osteoporosis indication was based on a 2-year, double-blind, randomized trial that showed that the estradiol-levonorgestrel patch was associated with significant maintenance of bone density compared to placebo. ■