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SPECIAL FEATURE

Burnout Syndrome Among Critical Care Professionals: A Cause for Alarm

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Dr. Chlan reports that she receives grant/research support from Hospira.

Clinicians who work in the intensive care unit (ICU) gravitate toward that particular setting because of the fast-paced, high-tech, challenging work in that environment. The life-and-death struggles can be exhilarating as well as emotionally and physically draining. This fast-paced, demanding, and stressful environment can also lead to a common syndrome among ICU clinicians: burnout. This special feature will describe burnout syndrome, identify factors that lead to burnout, discuss protective factors for allaying burnout, and provide some strategies that clinicians have used in their careers to maintain balance and resilience in a very demanding profession. While burnout occurs in any occupation, this paper will focus on ICU nurses and physicians.

CHARACTERISTICS OF BURNOUT

Burnout syndrome is a psychological state resulting from prolonged exposure to job stressors.[1] While burnout is a debilitating condition that can develop in anyone, regardless of occupation, ICU clinicians are at greater risk of developing burnout due to the chronic stress of the immediate work environment and the inherent stressful nature of critical care.[2] Defining burnout can be elusive, but there are several commonly accepted descriptions. Burnout is referred to as an occupation-induced psychological syndrome that is the extreme opposite of engagement.[3] Others view burnout as disillusionment deep within the very essence of an individual — the collapse of the human spirit.[4] There are three generally agreed-upon characteristics of burnout: 1) high emotional exhaustion; 2) high depersonalization,

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cynicism, or detachment; and 3) low levels of personal effectiveness or accomplishment.

ICU nurses have been studied more extensively over the past several years with respect to incidence of burnout due to their presence in large numbers on the critical care units and their close proximity to and responsibilities for around-the-clock patient care. However, the shortage of intensivists and the demands for 24/7 ICU coverage have led to an increased awareness and recognition of burnout among physicians as well. While it is impossible to survey every ICU nurse and physician worldwide to obtain an estimate of the percentage of clinicians with burnout syndrome, some cross-sectional surveys have reported 50% of ICU physicians and 33% of critical care nurses suffer from severe burnout syndrome.[1]

While both nurses and physicians experience burnout, development of the syndrome arises from different sources in the two groups of professionals. For intensivists, a high number of working hours (defined as number of night shifts and time since last vacation) is one of the primary contributors[5] to burnout. For ICU nurses, the organizational culture and moral distress surrounding end-of-life issues were identified as the main contributors to burnout syndrome.[1] Interestingly, conflicts in the ICU environment with colleagues or with interdisciplinary colleagues were predictors of burnout for both nurses and physicians.[5]

SNAPSHOT OF ICU NURSE BURNOUT

The main contributor to emotional exhaustion in ICU nurses is stress from the high patient acuity.[2] Critical care nurses are asked to manage multiple aspects of patient care, typically care for two patients during a shift, and are expected to make sound clinical decisions and react quickly.

Another key contributor for ICU nurse burnout is the morally distressing situations encountered on a daily basis in the work setting. Moral distress can be defined as when people are unable to act in accordance with what they believe to be ethical, or when they act in a way that is contrary to their personal or professional values.[6] The distress comes when one's integrity and authenticity are undermined. Typically, moral distress is not identified as a contributor to ICU physician burnout as physicians are the professionals who make final decisions regarding a plan of care. While nurses are part of the care team, they usually are not involved in this final decision making about plans of care. Moral distress usually arises around the decision to continue aggressive treatment of patients when nurses feel the actions are futile. The unnecessary prolongation of life is one of the most stressful situations for ICU nurses, particularly when it goes against a patient's known wishes.[7]

Critical care nurses many times are caregivers not only for patients but for family members as well. This can also contribute to emotional exhaustion and "compassion fatigue" when nurses identify on a personal level with patients and their family members in that they absorb their suffering and pain.[8]

Emotional exhaustion contributes to depersonalization, which is a coping mechanism in response to emotional overload.[2] Nurses become detached from patients, family members, and their colleagues; they put distance between themselves and the work setting. A cynical attitude may develop in response to feeling powerless and prevent the nurse from any action.[2]

Lastly, feelings of ineffectiveness and lack of personal accomplishments also contribute to burnout in ICU nurses. Many ICU nurses have very high standards of care and expectations for themselves that they may not be able to meet.[2] Lack of personal accomplishment can also arise when nurses perceive that physicians do not value their viewpoint and expertise, and are omitted from decision making about patient care.

SNAPSHOT OF PHYSICIAN BURNOUT

Deterioration of physician well-being from excessive stress is a widespread problem.[9] There is a direct link with burnout to substance abuse (alcohol and drugs), job turnover, marital problems, and low morale.[9] Physicians face pressures from many sources: recognition from peers as being a hard worker, service to others before self, exhaustion leading to loss of empathy, and blaming patients for their conditions. Other factors such as steadily declining incomes and the devaluation of the doctor-patient relationship also contribute to burnout. Many physicians feel like they have to spend too much time on the "business" side of medicine.[9] In a survey by Chopra and colleagues, 80% of practicing physicians reported moderate-to-high levels of emotional exhaustion, 93% moderate-to-high levels of depersonalization, and 75% low-to-moderate levels of personal achievement.[10] Among intensivists, a heavy number of hours worked without time off and conflicts with fellow intensivists or nurses were associated with higher burnout scores.[5]

In addition, doctors have high rates of mental health problems, including depression, misuse of prescription drugs, and burnout, particularly among female physicians.[11] Higher rates of mental health problems appear to be more prevalent among younger physicians in the 30-39 year age category,[11] which does not bode well for the health and well-being among the physicians of tomorrow.

Risks factors contributing to potential mental health problems among physicians include clinical occupational factors and structural occupational factors.[11] Clinical factors are those stressors that emanate from the emotional demands of working with patients and dealing with anxiety, suffering, and death.[11] Structural factors contributing to risk of mental health issues for physicians include heavy workload and working hours, sleep deprivation, and unpredictable hours contributing to psychological distress.[11] Individual personality factors such as being self-critical and engaging in unhelpful coping strategies (i.e., emotional distancing) can contribute to psychological distress, burnout, and mental health problems.[11]

WHAT ARE THE CONSEQUENCES OF BURNOUT?

Perhaps the most prominent of the consequences of burnout syndrome among ICU professionals is that burnout can lead to staff turnover and lost productivity. Burnout can lead ICU nurses to consider leaving the profession entirely, which does not remedy the continued and projected nursing shortage. Patient care and communication can suffer when ICU professionals are "disengaged" from their colleagues, patients, family, and work environments. The work of Brooks and colleagues details the mental health problems facing physicians who are emotionally exhausted, including addiction to drugs and alcohol.[11] Suicide is also an outcome of mental health problems tied to emotional exhaustion.[12]

The stakes are too high not to be concerned about ICU clinicians' mental health and well-being. While the evidence presented thus far may seem dismal, there is hope to remedy burnout syndrome. Nurses and physicians can personally employ a number of strategies to buffer against burnout and to strengthen their own mental health. Some of these strategies are described below.

PROTECTIVE AND PROACTIVE STRATEGIES FOR BURNOUT SYNDROME

For ICU nurses, a supportive environment where nurses feel their voice is heard and their opinions are respected is key for preventing nurse burnout.[2] The availability of counseling services and time to debrief are also important factors in a supportive work environment for nurses. Nurses need to take professional responsibility to support one another in their everyday work environments. This can be accomplished with a "buddy system" where nurses can provide encouragement and support to one another.[2] Recognizing nurses for their many contributions to patient and family care with meaningful awards and recognitions are also important burnout-buffering strategies.

Nurses need to take personal responsibility for their own health and well-being. The tried and true strategies of a healthy lifestyle, taking breaks and vacations, eating a balanced diet, and getting enough rest and sleep apply to ICU nurses as well as every other group of professionals.

The presence of resilience has been found to play a role in healthier psychological profiles of ICU nurses and also in physicians, and can serve as a buffer for burnout. Resilience is a multidimensional characteristic that embodies the personal qualities that enable one to thrive in the face of adversity.[13,14] Resilience can be learned through cognitive behavioral therapy and factors such as temperament, family bonds, external support systems, and personal qualities (optimism, faith, striving towards personal goals).[14]

For physicians, the ability to remain focused on what is important in life contributes to well-being.[9] Strategies such as setting limits and

self-awareness of boundaries, spending time with friends and family, maintaining self-care through exercise, maintaining self-care through relaxation, and having a healthy philosophical outlook through humor are all effective in buffering against physician burnout.[9] Among surgeons who responded to a national survey, those who placed a greater emphasis on work-life balance, finding meaning in work, maintaining a positive outlook, and focusing on what is important in life were less likely to have burnout.[15]

SUMMARY AND CONCLUSIONS

Burnout is a common syndrome among ICU nurses and physicians. Burnout can lead to disengagement and cause skilled clinicians to leave the ICU setting or their professions altogether, particularly among nurses. The good news is that there are a number of evidence-based strategies for ICU clinicians to integrate into their daily lives to provide a buffer against burnout.

The most essential skill for any ICU professional may be finding personal balance. This idea of balance will mean different things to different ICU professionals. While not rocket science, the time-honored methods of setting limits, spending quality time with friends and family, exercising, relaxing, and maintaining a sense of humor can go a long way to promoting personal health and well-being. There will never be enough ICU physicians and nurses, and there will never be enough hours in the day to accomplish everything on our "to do "lists. We need to care for ourselves and encourage our colleagues to do so as well. Only then will we have the emotional and physical energy to effectively care for the increasing numbers and acuity of our patients and their family members. I challenge every ICU professional to take responsibility to recognize his/her own personal limits, take mini-recovery breaks, practice relaxation such as mindfulness or deep breathing, exercise regularly, rest and get adequate sleep, eat a healthy diet, and engage in enjoyable leisure activities. No one is invincible! We should not expect this of ourselves or our colleagues. ■

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ABSTRACT & COMMENTARY

ICU Feeding Strategy and Acute Lung Injury Outcomes

By Betty Tran, MD, MS

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

SYNOPSIS: Survivors of acute lung injury (ALI) performed below predicted values on a number of physical and cognitive performance assessments at 6 and 12 months. Initial trophic vs full enteral feeding during the first 6 days of mechanical ventilation had no significant effect on these long-term outcomes.

SOURCE: Needham DM, et al. Physical and cognitive performance of acute lung injury patients one year after initial trophic vs full enteral feeding: EDEN trial follow-up. *Am J Respir Crit Care Med* 2013;188:567-576.

The EDEN trial was a multicenter, randomized, open-label study that sought to compare the effect of initial trophic vs full enteral feeding for the first 6 days of mechanical ventilation on clinical outcomes of patients with acute lung injury (ALI).[1] Inclusion criteria included patients with ALI (defined by the presence of bilateral pulmonary infiltrates, PaO_2/FiO_2 < 300 mmHg, and the absence of left atrial hypertension) within 48 hours of onset, on mechanical ventilation for less than 72 hours, who were eligible for enteral feeding. Despite achieving a marked difference in total protein and caloric intake between the trophic and full feeding groups within 6 days of randomization (400 vs 1300 kcal/day), the investigators found no significant difference in short-term outcomes such as ventilator-free days or 60-day mortality. In this ancillary study, Needham and colleagues sought to assess longer-term physical and cognitive outcomes of ALI survivors at 6 and 12 months and the effect of initial trophic vs full enteral feeding on the same outcomes.

After excluding patients with baseline cognitive impairment, who were non-English speakers, homeless, or < 18 years of age, 174 patients with ALI from 12 hospitals participated in a series of physical and cognitive tests at 6 and 12 month follow-up. The primary physical performance outcome was the 12-month 6-minute walk test (6MWT) as a percent of the predicted value; a number of secondary physical outcomes were also assessed. The primary outcome for cognitive performance was the presence of "cognitive impairment" at 12 months, defined as having either one cognitive test with a score ≥ 2 standard deviations (SD) or at least two tests with a score ≥ 1.5 SD below population norms. A battery of cognitive tests that constituted individual secondary outcomes evaluated executive function, language, immediate and delayed memory, verbal reasoning and concept formation, and attention and working memory.

The mean 6MWT at 12 months was 66% predicted (± 25%) with overall small but statistically significant improvements in most physical performance parameters from 6- to 12-month follow-up. At 12 months, 25% of ALI survivors had cognitive impairment, which was a significant improvement from 36% at 6 months (P = 0.001). In all cognitive tests except Digit Span (evaluates attention and working memory), there was also significant improvement in mean scores between 6 and 12 months.

When patients who were randomized to initial trophic enteral feeds were compared to those receiving full feeds, there was no significant difference in mean percent predicted 6MWT values (63% [± 25%] vs 70% [± 24%], P = 0.146), proportion of patients with cognitive impairment (29% vs 20%, P = 0.311), or in all secondary outcomes at 12 months even after adjustment for multiple covariates.

■ COMMENTARY

There were several notable strengths in this trial. Sample size was relatively robust compared to prior studies involving long-term outcomes in ALI survivors. A detailed battery of physical and cognitive testing was performed in-person by trained personnel who were blinded to each patient's treatment allocation. Concerted efforts resulted in a minimal loss to follow-up. *A priori* statistical plans were formulated to attempt to minimize confounding and effect modification by several other variables. Known ICU interventions that have been shown to improve outcomes were employed across the board, including ARDSNet lung protective ventilation, fluid-conservative management strategies, and targeted blood glucose control. Overall, ALI survivors had small physical and cognitive improvements over time, but still performed below expected on physical and cognitive testing 1 year after ALI onset regardless of the average protein and total caloric intake they received early in their ICU course.

This study contributes to our growing but still limited knowledge on the optimal timing, formulation, and amount of nutrition in the ICU. Rapid muscle catabolism related to systemic inflammation with the potential to cause muscle atrophy and severe nutritional deficits has been described in early critical illness.[2] However, whether nutrition can modify these processes and via what mechanisms is not known. We have yet to show a nutritional intervention in this acute phase that can alter these effects and result in improved short- or long-term patient outcomes. In one such attempt, the Omega study, supplementation with omega-3 fatty acids, γ-linolenic acid, and other antioxidants that could theoretically modulate the systemic inflammatory response not only resulted in no patient benefit but was associated with more days on the ventilator, in the ICU, and organ failure.[3] As we continue to expand our understanding of risk factors and treatment strategies that have an impact on long-term outcomes in survivors of ALI and critical illness, it is likely that nutrition is but one aspect in the overall trajectory of recovery for these patients. It will be interesting to see how important a role it plays in comparison to

other interventions such as early physical and occupational therapy and minimizing sedation and delirium. ■

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ABSTRACT & COMMENTARY

The Vexing Problems of Lung-Protective Ventilation: Asynchrony, Work of Breathing, and Sedation

By Richard H. Kallet, MS, RRT, FAARC, FCCM

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Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: This single-center, prospective, observational study examined the effects of clinician adjustments in ventilator settings or sedation/analgesic dosing on "breath stacking" (an inspiratory effort that causes the ventilator to deliver two consecutive breaths without an intervening expiratory phase). Although both strategies significantly reduced the incidence of breath stacking, ventilator adjustments were markedly superior.

SOURCE: Chanques G, et al. Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. *Crit Care Med* 2013;41:2177-2187.

Thirty mechanically ventilated patients with acute respiratory failure were enrolled in the trial. Eligible patients had evidence of "severe asynchrony" as measured by the Asynchrony Index (AI) and defined as > 10% of all inspiratory efforts resulting in breath stacking. Continuous evaluation of ventilator waveforms, as well as sedation and pain levels, were monitored in 30-minute periods before and after 50 clinician-directed decisions were made on how to treat breath stacking. Patients were uniformly managed with volume assist-control ventilation at a tidal volume (Vt) of 6 mL/kg predicted body weight and a set peak inspiratory flow rate of 60 L/min (0.5 sec inspiratory time) and trigger sensitivity of -2 cm H_2O. A sedation/analgesic protocol initially targeted a RASS (Richmond Agitation and Sedation Scale) score of 0 to -2. Pain was assessed during daily sedation interruptions and treated with opiate boluses and a 50% infusion rate increase. Likewise, bolus sedation was used for RASS scores > +2.

Sedation and analgesic adjustments were highly effective in reducing agitation and pain and coincided with a significant reduction in AI from 41% to 27%. In contrast, increasing the ventilator inspiratory time to 1 second (by adding an end-inspiratory pause) or changing to pressure support ventilation greatly reduced the AI score from 38% to 2%. However, use of pressure support ventilation resulted in a significant increase in Vt.

■ COMMENTARY

The puzzle of patient-ventilator asynchrony goes back to the 1960s when it was observed that setting a physiologic Vt of 7 mL/kg in conscious, critically ill patients frequently produced subjective complaints of dyspnea ("inadequate chest expansion").[1] Thus, patient perception of "volume starvation" was largely responsible for the practice of using a generous Vt (10-15 mL/kg). Since the mid-1980s, numerous studies have investigated patient-ventilator interfacing and its effect primarily on patient work of breathing (WOB). This research has both enriched our understanding of patient-ventilator synchrony and resulted in substantial improvements in ventilator technology.

Four important aspects to this discussion are: 1) patient Vt demand and inspiratory flow represent the effects of global inspiratory muscle shortening and the velocity of muscular contraction; 2) when the corresponding ventilator-set Vt and flow are below demand, an additional workload is imposed on the patient's respiratory muscles;

3) neural-mechanical dissociation (the primary cause of dyspnea) occurs when effort and muscle tension are both disproportionate to and out of phase with chest excursion (the response to which is a reflexive increase in respiratory drive); and 4) neural inspiratory off-switch occurs at the Vt "targeted" by the patient. Therefore, mismatching in Vt, inspiratory flow, and inspiratory time between patient demand and ventilator settings causes increased patient WOB and "asynchrony." In addition, emotions and bodily sensations are expressed partly through changes in the breathing pattern, so that asynchrony is exacerbated by pain, discomfort, anxiety, and delirium. Therefore, sedation and analgesia play an immense role in promoting synchrony.

Restricting Vt while providing adequate inspiratory flow (e.g., > 60 L/min) in an effort to limit imposed WOB necessitates an abnormally brief inspiratory time. This in itself potentiates breath stacking. Unfortunately, increasing the pause time can increase patient effort and induce acute negative-pressure pulmonary edema because continued vigorous inspiratory efforts occur against an occluded circuit.[2] Pressure support ventilation may alleviate breath stacking but inadvertently may promote ventilator-induced lung injury from poor Vt control. Moreover, during lung-protective ventilation, pressure modes are not necessarily superior to volume modes with a high flow rate at a comparable Vt.[3]

Asynchrony accompanying lung-protective ventilation may not have a satisfactory solution. However, a practical tool for balancing the competing problems of excessive Vt delivery, excessive WOB, and excessive sedation is simply to utilize a brief trial of continuous positive airway pressure. This allows clinicians to assess both the magnitude and variation in Vt and flow rate generated by patients, and thereby determine how far these deviate from clinician goals. Also, intermittently executing an expiratory hold (prior to an inspiratory effort) allows an estimate of inspiratory muscle pressure. This can be used to assess patient effort in response to therapeutic interventions. By using this simple assessment technique, clinicians can make clear decisions that balance the competing priorities of lung-protection, WOB, and sedation that often are at odds with one another during mechanical ventilation.

■ EDITOR'S COMMENTARY
DAVID J. PIERSON, MD

Patient-ventilator asynchrony is a huge problem in respiratory care, often constituting a practical barrier to the implementation of lung-protective ventilation.[4] Its potential adverse effects are numerous and important:[5]

- Ineffective ventilation
- Hypoxemia
- Lung over-distension
- Dynamic hyperinflation
- Increased work of breathing
- Patient discomfort
- "Fighting the ventilator"
- Distress for family members and others at the bedside
- Conflict among team members
- Excessive administration of sedatives and neuromuscular blocking agents
- Respiratory muscle dysfunction
- Confusion with respect to readiness for weaning
- Prolongation of mechanical ventilation
- Neuromuscular complications of prolonged immobility.

Breath stacking, also known as double-triggering, is an especially troublesome manifestation of asynchrony in patients on lung-protective ventilation using volume-targeted, assist-control ventilation. The latter remains the most widely used ventilation mode in the world, and knowing how to adjust it properly to minimize asynchrony is important.[6] As the study by Chanques et al shows, and Kallet emphasizes in the above discussion, increasing sedation is much less effective in reducing patient-ventilator asynchrony than adjusting the ventilator settings when breath stacking occurs. ■

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CME/CNE Questions

1. Which of the following statements is true regarding burnout syndrome in ICU clinicians?

a. Only ICU nurses are susceptible to burnout.
b. There is no evidence of burnout syndrome among intensivists.
c. Both ICU nurses and physicians are susceptible to burnout.
d. Burnout can easily be overcome with adequate staffing patterns.
e. All of the above

2. Based on the evidence presented on burnout, which of the following strategies is effective in buffering against burnout syndrome?

a. Resilience training through cognitive behavioral therapy
b. Higher pay for all clinicians
c. Limiting family visiting hours
d. Working more rotating shifts
e. Requiring the nurse manager and the medical director to socialize

3. Which of the following is true about survivors of acute lung injury (ALI) at 6 and 12 months after ALI onset?

a. They perform below predicted values for 6-minute walk distance.
b. They have some improvement in physical performance over time when comparing 6- to 12-month follow-up values.
c. Approximately 1 out of 4 has evidence of cognitive impairment at 12 months.
d. Only a and c are true
e. A, b, and c are true

4. In the Needham et al study, compared to patients randomized to initial trophic feeds within 6 days of ALI onset, patients who were randomized to receive full enteral feeding:

a. had improved physical, but not cognitive, function at 6 and 12 months.
b. had improved cognitive, but not physical, function at 6 and 12 months.
c. had both improved physical and cognitive function at 6 and 12 months.
d. had no significant improvement in physical or cognitive function at 6 and 12 months.
e. were inherently different despite statistical adjustment and no conclusions can be drawn with regard to their long-term outcomes.

5. Which of the following statements does *not* reflect the mechanisms that promote patient-ventilator synchrony?

a. A patient's Vt demand and his/her generated inspiratory flow rate reflect the effects of respiratory muscle contraction.
b. Neural inspiratory time is largely determined by the ventilator trigger sensitivity.
c. A ventilator-set Vt below that demanded by the patient places an additional load on the breathing muscles.
d. Breath stacking often occurs when the neural inspiratory time is greater than the ventilator-set inspiratory time.
e. Neural inspiratory time "switches off" when the Vt targeted by the patient has been achieved.

6. All of the following are true regarding the study of patient-ventilator asynchrony by Chanques et al *except*:

a. Ventilator graphics were used to assess breath stacking.
b. Patients were targeted to a RASS score of 0 to -2.
c. The Asynchrony Index captures the number of "uncaptured" spontaneous breathing efforts over 30 minutes.
d. Asynchrony could be treated successfully by increasing the pause time.
e. Asynchrony could be treated by changing the mode to pressure support.

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.

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Goldilocks Unable to Find Amount of Antioxidants That's Just Right

Source: Bjelakovic G, et al. *JAMA* 2013; 310:1178-1179.

The observation that excess oxidative stress is associated with diverse pathologic consequence has been consistently coupled with the obvious next intellectual step: antioxidants *should* be beneficial to prevent these consequences. Unfortunately, no Goldilocks has stepped forward to inform us which antioxidant is too much, which is too little, and which is just right. Or maybe the antioxidant hypothesis is just a fairy tale, after all?

This is not the first time that observational hypotheses have disappointed. In two clinical trials of antioxidant supplementation in persons at risk for lung cancer (combined n > 45,000), the first trial found an *increase* in lung cancer and mortality, and the follow-up trial was discontinued almost 2 years early because of similar outcomes.

This most recent Cochrane systematic review included 78 trials (n = 296,707) performed in both primary and secondary prevention modes. The "bottom line" is worth quoting: "Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with *higher* all-cause mortality." Some naysayers would suggest that we have not yet fulfilled the Goldilocks systematic approach: Maybe we used too little, maybe we used too much, or maybe we used the wrong formulation, and have not yet found the approach that's "just right." For now, the science does not support a role for antioxidants in primary or secondary prevention. ■

Antipsychotics Are Associated with Increased VTE Risk

Source: Wu CS, et al. *J Clin Psychiatry* 2013;74:918-924.

Antipsychotics have suffered a beleaguered course of late: literature showing little efficacy advantage of newer vs older agents, concerns about increased mortality associated with their use, etc. A recent report suggests that antipsychotic treatment is also associated with a clinically meaningful increase in risk for venous thromboembolism (VTE), comprised of deep vein thrombosis plus pulmonary embolism.

Wu et al performed a case-control study of enrollees in the National Health Insurance Research Database of Taiwan to compare cases of confirmed VTE (n = 2162) with age-matched controls without VTE (n = 12,966). Initial analysis looked simply at the relative risk of antipsychotic use in persons with VTE vs controls. Second-step analysis adjusted for confounders.

Overall, the adjusted odds ratio for VTE in current antipsychotic users was 1.52 (i.e., current users were 52% more likely to experience VTE than controls); the odds ratio was substantially worse (3.26: a more than 3-fold increase in risk) for new users. These concerning results were attained even after correction for confounding factors such as utilization of thrombogenic medications (e.g., oral contraceptives) and medical comorbidities associated with increased VTE risk (e.g., congestive heart failure). Analysis of different classes of antipsychotics did not find any particular distinction among them. The mechanism by which antipsychotics might increase VTE risk is uncertain, although the authors posit that antipsychotic-induced sedation could lead to less physical activity with subsequent venous stasis. In any case, these data suggest vigilance for VTE in persons prescribed antipsychotics, especially in the early months of use. ■

Physician Visits for Itching

Source: Shive M, et al. *J Am Acad Dermatol* 2013;69:550-556.

If results from the National Ambulatory Medical Care Survey conducted by the CDC are correct, pruritus as a presenting complaint in ambulatory care may merit more of our attention. In a retrospective review of data from 1999-2009, there were approximately 7 million office visits per year in which pruritus (or itching) was indicated as a presenting symptom. In comparison, there were almost 18 million visits per year for low back pain. Since itch may or may not have been specifically indicated when syndromes such as a drug allergic reaction occur, the authors suggest that these numbers likely *underestimate* the true prevalence of pruritus.

The consequences of pruritus may range from minor nuisance to intolerable. Indeed, patients taking opioid analgesia frequently mention pruritus as a treatment-limiting adverse effect. Fortunately, clinicians have a diversity of agents to treat pruritus, including multiple generations of antihistamines as well as steroids (topical and systemic). Finally, it has been

recognized for more than 2 decades that doxepin — traditionally used as an antidepressant — has antihistaminic potency as much as 50 times greater than the most potent "traditional" antihistamines such as hydroxyzine. Because of this antihistaminic potency, doxepin is often used in refractory urticaria, when other antihistamines have failed, even though sedation is common at typical therapeutic doses. ■

Consequences of Non-Adherence in Treated Hypertensives

Source: Cummings DM, et al. *J Am Soc Hypertens* 2013;7:363-369.

The relationship between elevated blood pressure (BP) and stroke is linear and continuous. An abundance of clinical trial data indicate that treatment of hypertension (HTN) by means of numerous diverse classes of antihypertensives lowers stroke risk by ≥ 40%. Clinical trials, however, are not "real life." The Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study is examining a large population (n = 30,239) of southeastern men and women with HTN. Their assessment of the relationship between self-reported degree of antihypertensive medication adherence and serious outcomes (stroke/TIA) from a subset population (n = 15,071) is quite sobering.

During a 5-year window of observation, study participants were grouped into four categories of adherence using the Morisky scale, which translates into general groupings of high, good, moderate, and low adherence. Perhaps not surprisingly, mean systolic BP in the high adherence group was substantially better than the low adherence group (131 mmHg vs 138 mmHg). Incidence of stroke or TIA was 8% higher in the lowest adherence group compared to the highest. Good BP control has meaningful payoff; every decrement of adherence less than that is costly. ■

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Long-Term Risk-Reduction Benefits of Sigmoidoscopy and Colonoscopy

Source: Nishihara R, et al. *N Engl J Med* 2013;369:1095-1105.

Participants from two large observational studies provide an opportunity to evaluate the risk reduction accrued from either colonoscopy (COL) or sigmoidoscopy (SIG). The Nurses' Health Study (n = 121,700 female nurses) and the Health Professionals Follow-up Study (n = 51,529 male health professionals) have more than 20 years' prospective follow-up of their participants. During this interval, there were 1185 cases of colon cancer and 474 deaths from colon cancer.

Skeptics have long held fast to the tenet that SIG had an advantage over COL: proven risk reduction for colon cancer mortality for the former. Although the intuitive additional advantage of examining the entire colon with COL seemed a no-brainer, purists argued that whether COL was truly better than SIG was not yet proven, and that since COL was associated with greater risks (perforation, adverse effects from sedation, etc.), there was reasonable basis to continue with SIG as a preferred method. In accord with this philosophy, noting the many missed opportunities for colon cancer screening and prevention, advocacy groups rallied around the call-to-action, "The best colon cancer screening test is whichever one you can get done!"

These data may change that perspective, since the risk reduction for colon cancer death was almost twice as great for COL as SIG (hazard ratios, 0.59 vs 0.32). The "no-brainer" part of the equation was also resoundingly confirmed: COL reduced mortality from proximal colon cancer by more than half compared to no risk reduction through SIG. ■

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Warfarin Outperforms Dabigatran in Patients with Mechanical Heart Valves

Source: Eikelboom JW, et al. *N Engl J Med* 2013;369:1206-1214.

The atrial fibrillation (AF) headlines have been filled with celebration over the efficacy of factor Xa inhibitors (e.g., rivaroxaban, apixaban) and direct thrombin inhibitors (e.g., dabigatran) for prevention of thrombotic events. Since warfarin — though highly effective, exhaustively studied, and time-tested — also has distinct clinical burdens (e.g., need for monitoring, food interactions, drug interactions), agents that were at least as efficacious for thrombotic risk reduction — with fewer of these same clinical burdens — were welcomed.

Success in AF, however, does not necessarily translate into other pathologies. Eikelboom et al studied patients with recent mitral or aortic mechanical valve replacement (n = 252). Subjects were randomized to dabigatran or warfarin. About one-fourth of these patients also had AF.

The trial had to be discontinued early because of untoward events in the dabigatran group: stroke occurred in 5% of the dabigatran group vs none in the warfarin group, and major bleeding was twice as common on dabigatran (4% vs 2%). Although earlier trials in animals were encouraging, these data indicate that warfarin is safer and better tolerated in patients with recent surgery for prosthetic mechanical heart valves. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Reglan Safe in Pregnant Women for Nausea and Vomiting

In this issue: Reglan safe in pregnancy; battle brewing over naming of biosimilar drugs; and FDA actions.

Reglan safe in pregnancy

Use of the anti-nausea medication metoclopramide (Reglan) in pregnancy is not associated with an increased risk of major congenital malformations, spontaneous abortion, or stillbirth. These were the findings of large, register-based cohort study from Denmark. The safety of metoclopramide in pregnancy has been of concern because it is increasingly used to treat pregnant women with nausea and vomiting. Metoclopramide-exposed pregnant women were matched with unexposed women in a 1:4 ratio, with more than 40,000 exposed women in the cohort, of whom more than 28,000 received the drug in the first trimester. The drug was not associated with major malformations or any of more than 20 individual malformations. There was no increase in spontaneous abortion, stillbirth, preterm birth, low birth weight, or fetal growth restriction (*JAMA* 2013; 310:1601-1611). ■

Battle over naming of biosimilar drugs

A battle is shaping up between biotech companies and the Generic Pharmaceutical Association (GPhA) over the naming of biosimilar drugs. Biosimilars, or "follow-on biologics," are products whose active ingredient is an approved version of a previously approved biopharmaceutical. Since biologics are generally manufactured in a complex process that may include molecular clones and proprietary cell lines, it is virtually impossible for the manufacturers of a biosimilar to match the process step-by-step. This results in small differences between the innovator product and the follow-on product (hence the name "biosimilar"). With billions of dollars of revenue at stake, biotech companies, such as Genentech and Amgen, have been lobbying federal and state legislators to tighten the rules regarding use of biosimilars. There has also been concern that the FDA might prohibit biosimilar manufacturers from using the same generic name as the original drug, a move that biotech companies would endorse and the GPhA would strongly oppose. A bipartisan group of senators recently entered the fray by penning a letter to the FDA urging the agency to allow biosimilars to share the name of the innovator product. Led by Republican John McCain and Democrats John Rockefeller and Tom Harkin, six senators urged the FDA to follow the intent of the Biologic Price Competition and Innovation Act, suggesting that if biosimilars were not allowed to share the same name it would undermine "the safety and accessibility of affordable biosimilars." The FDA had been in support of allowing biosimilars to share generic names, but the sudden removal of a page from the FDA website that contained a 2006 statement supporting same-name biosimilars prompted the concern of the senators. ■

FDA Actions

The FDA is recommending that hydrocodone-containing pain medications (Vicodin, Norco,

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Lortab, and others) be upgraded from schedule III to schedule II. The move would put significant restrictions on the drugs, including requiring a physician signature for each prescription, no refills, and no phone or fax prescriptions. Hydrocodone would join other powerful opioids including oxycodone, morphine, fentanyl, and methadone in the more restricted schedule II category. The FDA is reacting to the epidemic of prescription drug abuse and addiction that has decimated some communities in this country and has led to the overdose by tens of thousands, including teenagers and young adults. Prescription drug overdoses now outnumber illegal drug overdoses 3:1. The Drug Enforcement Agency has been pushing for stronger controls on hydrocodone for years, but physician and pharmacy organizations have successfully argued that the change unfairly impacts legitimate patients and would increase physician and pharmacy workloads. Hydrocodone/acetaminophen combination drugs were the most frequently prescribed medications in the United States last year. The change is likely to take effect by mid-2014.

Meanwhile, the FDA has approved an extended-release hydrocodone product for the management of severe pain requiring daily, around-the-clock treatment. The drug is an extended-release formulation of hydrocodone that is dosed twice a day. It is available in six strengths — 10, 15, 20, 30, 40, and 50 mg capsules. Because of concerns of addiction and abuse, and the greater risk of overdose and death associated with extended-release and long-acting formulations, hydrocodone extended-release should be reserved for patients in whom alternative treatment options are ineffective, not tolerated, or one otherwise provides inadequate pain management. The approval of hydrocodone extended-release was controversial given that the drug is not packaged as a tamper-proof capsule, theoretically allowing it to be crushed, chewed, or even injected. Experience with abuse of extended-release oxycodone (OxyContin) prompted the FDA to require Purdue Pharmaceuticals to reformulate the drug into a tamper-proof capsule in 2010. Some in the FDA felt this new formulation of hydrocodone should be similarly packaged, but the drug was approved without such restrictions. Hydrocodone extended-release will be schedule II, and marketed by Zogenix Inc. as Zohydro.

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The FDA has approved two new drugs to treat pulmonary arterial hypertension (PAH). Macitentan is a dual endothelin-receptor antagonist, while riociguat is a first in class soluble guanylate cyclase stimulator. Macitentan is a once-daily pill that is approved to treat PAH. Its safety and efficacy was established in a 2-year, randomized, placebo-controlled trial of 742 patients. Patients in the active treatment group had delayed progression of the disease and improved symptoms. Macitentan is manufactured by Actelion Pharmaceuticals and will be marketed as Opsumit. Riociguat is also an oral agent given three times a day. It is approved for PAH and also for chronic thromboembolic pulmonary hypertension (CTEPH), the first drug to be approved for this latter indication. Safety and efficacy for PAH was shown in a trial of 443 patients in which treated patients had improved 6-minute walk times after 12 weeks. It was shown to be effective for CTEPH in a study of 261 patients in which treated patients had improved walk times at 16 weeks. Riociguat is marketed as Adempas by Bayer HealthCare.

An FDA advisory group has recommended approval of simeprevir and sofosbuvir, two long-awaited agents to treat hepatitis C virus (HCV). Both are oral drugs and have higher cure rates compared with currently available agents. Simeprevir is a protease inhibitor, similar to currently available agents such as telaprevir and boceprevir, while sofosbuvir is a new type of hepatitis c antiviral called a nucleotide analogue (or "nuke"). Sofosbuvir has been highly anticipated as clinical trials suggest that it results in sustained virological responses as high as 90%, and may eventually be part of an all-oral regimen for HCV along with ribavirin. The FDA is expected to approve both drugs by mid-December. Simeprevir will be marketed by Johnson & Johnson while sofosbuvir will be marketed by Gilead Sciences. ■