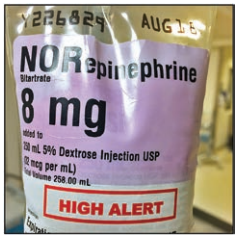
ANESTHESIOLOGY

Deborah J. Culley, M.D., Editor



Association between US norepinephrine shortage and mortality among patients with septic shock. JAMA 2017; 317:1433–42.

In 2011 the United States experienced a widespread shortage of drugs, including norepinephrine (noradrenaline). Norepinephrine is considered a standard vasopressor in the treatment of septic shock. This investigation aimed to determine if the 2011 norepinephrine shortage had an effect on in-hospital mortality in patients with septic shock. The investigators included more than 27,000 patients from 26 U.S. hospitals with shortages of norepinephrine in this retrospective cohort study. During the drug shortage period, the use of norepinephrine as first-line vasopressor to treat septic shock in hospitals with shortages of norepinephrine declined from 77 to 56% and this decrease was associated with an increased in-hospital mortality from 36 to 40% with an absolute mortality difference of 3.7% (95% CI, 1.5 to 6.0%, $P = 0.03$). The authors concluded that hospitals affected by the U.S. norepinephrine shortage had higher in-hospital mortality rates among patients treated for septic shock. *(Summary: Peter Nagele and Deborah J. Culley. Image: J. A. Fox, Brigham Health.)*

Take home message: Drug shortages can lead to a decrease in the use of preferred drugs in severely ill patients, resulting in increased mortality.

Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: A randomized clinical trial. JAMA 2017; 317:1321–8.

Dexmedetomidine has been proven to be effective in providing sedation among intubated patients, although little is known about the effect of dexmedetomidine on 28-day mortality or duration of ventilation in patients with sepsis. The study by Kawazoe *et al.* randomized 201 patients with sepsis to sedation with dexmedetomidine or a control group where sedation was provided without dexmedetomidine. Interestingly, there were no differences in 28-day mortality ($P = 0.20$), the number of ventilator-free days ($P = 0.20$), or length of intensive care unit stay ($P = 0.43$) between the two groups despite the finding that the dexmedetomidine group had better sedation control ($P = 0.01$). Subgroup analysis identified that patients with an Acute Physiology and Chronic Health Evaluation (APACHE II) score of 23 or higher randomized to the dexmedetomidine group had lower hospital mortality when compared to the control group ($P = 0.03$). The authors note that the study may have been underpowered to detect differences in 28-day mortality between the two treatment groups and suggest that further investigations are warranted. *(Summary: Deborah J. Culley. Image: J. P. Rathmell.)*

Take home message: Dexmedetomidine administration in the setting of sepsis may not decrease the number of ventilator-free days or 28-day mortality.

A nontoxic pain killer designed by modeling of pathological receptor conformations. Science 2017; 355:966–9.

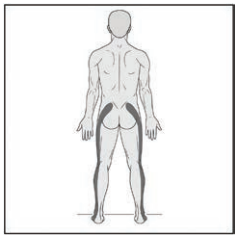
Toxicity and side effects of μ-opioids such as respiratory depression, use reinforcement, and constipation often limit the clinical utility of opioids. Recently, Spahn *et al.* attempted to address this issue by designing an opioid ligand that preferentially binds to the μ-opioid receptor under acidic conditions such as those that exist after tissue incision or during inflammation. Their ligand, (±)-N-(3-fluoro-1-phenethylpiperidin-4-yl)-N-phenyl propionamide (NFEPP), has a pKa of 6.8 supporting protonation and μ-opioid receptor activation only at subphysiologic pH. Biochemical studies confirmed that low pH was required for NFEPP to inhibit adenosine 3',5'-cyclic monophosphate accumulation *in vitro*. Using rodent models of incisional and inflammatory pain, the authors demonstrate that analgesia was only observed after injury. Importantly, NFEPP did not promote place preference indicating low abuse liability, and it did not slow gastrointestinal motility. This new approach of designing opioid molecules that are active only in injured tissues may lead to the availability of safe and powerful drugs with a reduced side effect profile. *(Summary: David Clark and Deborah J. Culley. Image: ©ThinkStock.)*

Take home message: In animal models, newer opioids designed to activate μ-opioid receptors only in the setting of pain may lead to pain relief from opioids with a reduced side effect profile.

A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA Psychiatry 2017; 74:399–405.

Ketamine has been used as an intravenous anesthetic agent for several decades. Recently, several groundbreaking studies have demonstrated that a subanesthetic dose of ketamine (typically 0.5 mg/kg IV given over 40 min) has immediate antidepressant effects in patients with treatment-resistant major depression. These discoveries have led to substantial excitement among the general public and mental health professionals alike. However, the use of ketamine for the treatment of depression is largely off-label and inadequately studied. In this special communication, the Council of Research Task Force on Novel Biomarkers and Treatments of the American Psychiatric Association released a timely consensus statement on the safety and effectiveness of using ketamine in the treatment of mood disorders. The statement covers patient selection, clinician experience and training (with an important corollary for anesthesiology), appropriate treatment setting, ketamine delivery, and adequate safety measures. This is an important document for any anesthesiologist who is actively involved in the care of psychiatric patients. *(Summary: Peter Nagele and Deborah J. Culley. Image: J. P. Rathmell.)*

Take home message: Interest in the use of ketamine as a treatment for depression has led to this consensus statement on the use of ketamine in the treatment of depression.



Trial of pregabalin for acute and chronic sciatica. N Engl J Med 2017; 376:1111–20.

Pregabalin is an approved treatment for several neuropathic pain conditions. This randomized, controlled trial investigated the effectiveness of pregabalin in the setting of acute and chronic sciatica. A total of 209 patients were randomized to receive 150 mg pregabalin per day (adjusted to a maximum of 600 mg) or placebo for 8 weeks. The primary outcome was the leg-pain intensity score where a score of 0 represents no pain and a score of 10 represents the worst possible pain. At week eight, there were no significant differences in leg-pain intensity scores between the pregabalin and placebo groups (mean difference 0.5; 95% CI, –0.2 to 1.2; $P = 0.19$). Interestingly, there were more adverse events reported in the pregabalin group when compared with that of the placebo group ($P = 0.002$). The authors conclude that pregabalin did not improve leg-pain scores associated with sciatica but resulted in significantly more adverse events. *(Summary: Peter Nagele and Deborah J. Culley. Image: G. Nelson.)*

Take home message: Pregabalin may not be effective in treating sciatic pain and may result in more adverse events, although the study may have been underpowered to detect a difference.

Prevalence and causes of attrition among surgical residents: A systematic review and meta-analysis. JAMA Surg 2017; 152:265–72.

The attrition of general surgery residents is thought to be a significant issue for surgical training programs. This systematic review and meta-analysis was designed to determine the prevalence of attrition of general surgery residents, the drivers for the attrition, and where these residents went after they left their surgical residency program. Overall the authors noted that 18% of general surgery residents left their general surgery residency program ($P < 0.001$). The two most common reasons for the high attrition rate included lifestyle issues and choosing to join another specialty. Interestingly, female residents were more likely to leave their general surgery programs when compared to male residents ($P = 0.008$). Among residents who left a general surgery program, 20% moved on to another general surgical program. Anesthesiology was the second most popular medical specialty when residents choose to leave general surgery ($P < 0.001$). The authors note that there is need for interventions to decrease the rate of resident attrition from general surgery residency programs. *(Summary: Deborah J. Culley. Image: J. P. Rathmell.)*

Take home message: There is a high prevalence of attrition among general surgery residents from their initial training program.

Effect of intensive vs moderate alveolar recruitment strategies added to lung-protective ventilation on postoperative pulmonary complications: A randomized clinical trial. JAMA 2017; 317:1422–32.

Pulmonary complications are common after cardiac surgery. Although lung-protective ventilation has now become the standard for perioperative mechanical ventilation (small tidal volume of 6 ml/kg of predicted body weight), it is unclear whether an intensive or moderate alveolar recruitment strategy influences the risk of postoperative pulmonary complications. In this trial, moderate recruitment consisted of three sustained lung inflations (30 s each) with 20 cm H_2O continuous positive airway pressure and an inspired oxygen fraction of 0.60. Intensive recruitment consisted of three cycles of lung inflation (60 s each) at a positive end-expiratory pressure of 30 cm H_2O, driving pressure of 15 cm H_2O, and inspired oxygen fraction of 0.40. In this single-center randomized controlled trial involving 320 patients undergoing cardiac surgery, the use of intensive alveolar recruitment was associated with a reduction in postoperative pulmonary complications: 15% *versus* 26% in patients receiving moderate recruitment (odds ratio, 1.86; 95% CI, 1.2 to 2.83; $P = 0.003$). There were no significant differences in reduction in hospital mortality and hospital length of stay with intensive alveolar recruitment on univariate analysis. These results should be confirmed in a large multicenter trial before implementing these findings in practice. *(Summary: Peter Nagele and Deborah J. Culley. Image: J. P. Rathmell.)*

Take home message: Intensive alveolar recruitment may decrease pulmonary complications in patients undergoing cardiac surgery.

Comparison of male vs female resident milestone evaluations by faculty during emergency medicine residency training. JAMA Intern Med 2017; 177:651–7.

Although many believe that gender bias is prominent in academic medicine, few studies have evaluated whether gender is associated with differences in resident evaluations. This longitudinal retrospective study examined the results of electronic, milestone-based evaluations for emergency medicine residents in eight residency programs. A total of 359 residents were evaluated with 285 faculty members contributing to the 33,456 direct observation evaluations. At the beginning of residency, female residents scored slightly higher than male residents; however, male residents achieved milestones at a rate of 13% faster throughout the remainder of their training when compared with their female counterparts. Interestingly, there were no differences in milestone scores based on the gender of the evaluator. The authors conclude that the difference is due to unconscious gender bias by the faculty independent of their own gender. Another explanation could be that implicit bias extends beyond the evaluation system to the program for training, which could result in females needing an additional 3 to 4 months of training to achieve the same milestone level. It is important that residency programs develop methods to prevent gender bias in both their evaluation systems and residency training programs. *(Summary: Cathleen Peterson-Layne and Deborah J. Culley. Image: ©Accreditation Council for Graduate Medical Education/American Board of Anesthesiology, reproduced with permission.)*

Take home message: Implicit gender bias may exist in residency programs and programs should adopt practices to prevent gender bias in all areas of the program.