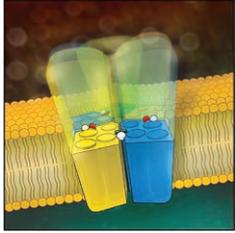


Key Papers from the Most Recent Literature Relevant to Anesthesiologists



GABA_A receptor signalling mechanisms revealed by structural pharmacology. *Nature* 2019; 565:454–9.

Modulators of γ -aminobutyric acid type A (GABA_A) receptors such as benzodiazepines and general anesthetics remain the cornerstones of clinical practice yet are known to have high abuse potential. This study reports on several high-resolution cryo-electron microscopy structures in which the full-length human $\alpha 1\beta 3\gamma 2L$ GABA_A receptor in lipid nanodiscs is differentially structurally modified by GABA_A receptors channel blockers, competitive antagonist, and agonists such as benzodiazepines. The classic channel blocker picrotoxin initially binds to an open channel pore and then stabilizes a closed or resting receptor state. The competitive agonist bicuculline occupies the agonist-binding sites and stabilizes the closed channel pore. Identification

of the molecular mechanism by which neurotransmitter binding to the $\beta 3+/\alpha 1-$ interface prompts a global rotation of extracellular domain regions, which may explain how different subunit types transduce conformational changes to their transmembrane domains. This study demonstrates the potential of cryo-electron microscopy to study the interactions of drugs with membrane-protein targets that may lead to the development of safer anesthetic and anxiolytic drugs. (Article Selection: Deborah J. Culley. Image: A. Johnson, C.M.I., Vivo Visuals.)

Take home message: This article may explain the structural framework that integrates previous research into the physiology and pharmacology of GABA_A receptor modulators.

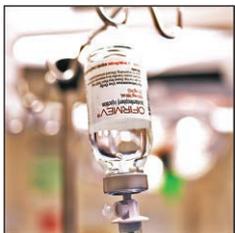


Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA* 2019; 321:969–82.

Tramadol for the treatment of pain in patients with knee osteoarthritis is recommended in guidelines from both the American Academy of Orthopaedic Surgeons and the American College of Rheumatology. This article examined the association of tramadol with all-cause mortality among patients with osteoarthritis. This study describes a propensity score–matched cohort study among UK adults aged 50 yr and older with a diagnosis of osteoarthritis. Patients received an initial prescription of tramadol ($n = 44,451$) or one of five other analgesics (naproxen = 12,397, diclofenac = 6,512, celecoxib = 5,674, etoricoxib = 2,946, or codeine = 16,922). The primary outcome was all-cause mortality within 1 yr after the initial tramadol prescription; 88,902

patients were included in the study after propensity score matching. During the 1-yr follow-up, 278 deaths occurred in the tramadol cohort for a death rate of 23.5 per 1,000 person-years. In the naproxen cohort, the rate difference was 9.7 deaths per 1,000 person-years (95% CI, 6.3 to 13.2); hazard ratio, 1.71 (95% CI, 1.41 to 2.07). The death rate was also higher for tramadol than diclofenac (36.2 per 1,000 vs. 19.2 per 1,000; hazard ratio, 1.88 [95% CI, 1.51 to 2.35]). Both celecoxib and etoricoxib also had lower death rates than the tramadol group, but there was no significant difference in all-cause mortality in the codeine group versus the tramadol group. (Article Selection: J. David Clark. Image: J. P. Rathmell.)

Take home message: Patients with osteoarthritis receiving a prescription of tramadol may have a higher 1-yr mortality when compared to patients who were prescribed nonsteroidal antiinflammatory drugs.



Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: The DEXACET randomized clinical trial. *JAMA* 2019; 321:686–96.

The choice of analgesics and sedatives may affect the development of postoperative delirium. This randomized clinical trial compared postoperative IV acetaminophen versus placebo plus IV propofol versus dexmedetomidine to determine their effect on postoperative delirium after cardiac surgery. Cardiac surgery patients were randomized to receive IV acetaminophen or placebo every 6 h for 48 h. They also received postoperative sedation with dexmedetomidine or propofol for up to 6 h (acetaminophen and dexmedetomidine: $n = 29$; placebo and dexmedetomidine: $n = 30$; acetaminophen and propofol: $n = 31$; placebo and propofol: $n = 30$). The

primary outcome was incidence of postoperative in-hospital delirium by the Confusion Assessment Method. Patients treated with IV acetaminophen had a significant reduction in postoperative delirium (10% vs. 28% placebo; hazard ratio, 2.8 [95% CI, 1.1 to 7.8]; $P = 0.01$). There was no significant difference in delirium among patients receiving dexmedetomidine versus propofol (17% vs. 21%; hazard ratio, 0.8 [95% CI, 0.4 to 1.9]; $P = 0.54$). (Article Selection: Martin J. London. Image: J. P. Rathmell.)

Take home message: Scheduled administration of IV acetaminophen after cardiac surgery when combined with IV propofol or dexmedetomidine may reduce postoperative delirium when compared to placebo.



Volatile anesthetics versus total intravenous anesthesia for cardiac surgery. *N Engl J Med* 2019; 380:1214–25.

Inhaled anesthetics may be cardioprotective, so their use might improve clinical outcomes in patients undergoing coronary artery bypass grafting (CABG). This 13-center, single-blind trial randomized patients undergoing elective CABG surgery to receive an anesthetic regimen containing the volatile anesthetic desflurane, isoflurane, or sevoflurane or a totally IV anesthetic. The primary outcome was all-cause mortality at 1 yr. Among the 5,400 randomized patients, 64% received on-pump CABG with a mean bypass time of 79 min. This trial was stopped for futility at the second interim analysis because there were no significant differences in death at 1 yr between the treatment groups. The death rate was 2.8% in the volatile anesthetics group and 3.0% in the total IV anesthesia group with a relative risk of 0.94 (95% CI, 0.69 to 1.29; $P = 0.71$). There was also no difference in the secondary outcomes, including the risk of myocardial infarction. (Article Selection: Beatrice Beck-Schimmer. Image: J. P. Rathmell.)

Take home message: The use of a volatile anesthetics in patients having CABG may not influence 1-yr mortality when compared to total IV anesthesia.



Patient blood management: Recommendations from the 2018 Frankfurt Consensus Conference. *JAMA* 2019; 321:983–97.

The Frankfurt International Consensus Conference was designed to address the need for evidence-based recommendations related to patient blood management. The scientific committee established 10 clinical recommendations and 12 research recommendations for preoperative anemia, red blood cell transfusion thresholds for adults, and implementation of patient blood management programs. The committee analyzed 145 studies, including 63 randomized clinical trials involving 23,143 patients and 82 observational studies with more than 4 million patients. There were strong recommendations to identify and address preoperative anemia before major elective surgery and for red blood cell transfusion thresholds in critically ill but stable patients in intensive care. The committee also recommended the development of comprehensive

patient blood management programs and the use electronic decision support systems to enhance appropriate red blood cell utilization. (Article Selection: J. David Clark. Image: J. P. Rathmell.)

Take home message: It may be reasonable to address preoperative anemia before elective surgery and utilization of electronic support systems to enhance appropriate use of red blood cells.



Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019; 380:1695–705.

Patients with aortic stenosis who are at intermediate or high risk for death experience similar outcomes with transcatheter aortic valve replacement and surgical aortic valve replacement. This article compares the two procedures in low-risk patients. Patients with severe aortic stenosis and low surgical risks ($n = 1,000$) were randomized to undergo either surgery or transcatheter aortic valve replacement with transfemoral placement of a balloon-expandable valve. The primary endpoint was a composite of death, stroke, or rehospitalization at 1 yr. This study used noninferiority testing (prespecified margin of 6 percentage points) and superiority testing among treated patients. They found the Kaplan–Meier estimate of

the rate of the primary composite endpoint at 1 yr to be significantly lower in the transcatheter aortic valve replacement group than in the surgery group (8.5% vs. 15.1%). The absolute difference was -6.6 percentage points (95% CI, -10.8 to -2.5 ; $P < 0.001$). The authors also found that patients in the transcatheter aortic valve replacement group had shorter hospital stays than those in the surgical group ($P < 0.001$). There were no significant differences in major vascular complications, new permanent pacemaker insertions, or paravalvular regurgitation between the transcatheter aortic valve replacement and surgical groups. (Article Selection: Martin J. London. Image: J. P. Rathmell.)

Take home message: In low-risk patients with severe aortic stenosis, the rate of composite death, stroke, or rehospitalization at 1 yr was significantly lower when having transcatheter aortic valve replacement when compared to surgery.



Effect of sustained inflations vs intermittent positive pressure ventilation on bronchopulmonary dysplasia or death among extremely preterm infants: The SAIL randomized clinical trial. *JAMA* 2019; 321:1165–75.

Sustained inflations may establish lung volume faster than short inflations among extremely preterm infants. This unmasked randomized controlled trial studied whether up to two sustained inflations at maximal peak pressure of 25 cm H₂O for 15 s, decreased the rate of bronchopulmonary dysplasia or death at 36 weeks' postmenstrual age (primary outcomes) when compared to control infants that received standard intermittent positive pressure ventilation. Planned enrollment was 600 infants born at 23 to 26 weeks' gestational age who required resuscitation. However, after a prespecified review of adverse

outcomes, the trial was stopped after enrolling 460 infants, 426 of which had completed the trial due to suggestion of harm in the sustained inflation group. In the experimental group, 137 infants (63.7%) died or survived with bronchopulmonary dysplasia versus 125 infants (59.2%) in the control group (adjusted risk difference, 4.7% [95% CI, -3.8% to 13.1%]; $P = 0.29$). More infants also died before 48 h of age in the experimental group: 16 infants (7.4%) versus 3 infants (1.4%) (adjusted risk difference, 5.6% [95% CI, 2.1% to 9.1%]; $P = 0.002$). (Article Selection: Laszlo Vutskits. Image: ©gettyimages.)

Take home message: Extremely preterm infants requiring resuscitation at birth may have better outcomes with standard intermittent positive pressure ventilation when compared to ventilation with sustained inflations.



Association between screen time and children's performance on a developmental screening test. *JAMA Pediatr* 2019; 173:244–50.

Excessive screen time is associated with delays in child development, but it is unclear if this association extends to lower performance scores on developmental screening tests, in part because children who score poorly on these tests may receive additional screen time as a behavioral management tool. This longitudinal cohort study used data from the All Our Families study to examine the directional association between screen time and child development in 2,441 children. Maternal reports were used to determine children's screen time at age 24, 36, and 60 months and developmental outcomes. The study found that higher levels of screen time at 24 and 36 months were associated with poorer performance

on developmental screening tests at 36 months (β , -0.08; 95% CI, -0.13 to -0.02) and 60 months (β , -0.06; 95% CI, -0.13 to -0.02), respectively. (Article Selection: Laszlo Vutskits. Image: ©gettyimages.)

Take home message: The results of this study support an adverse association between screen time and child development. The study authors recommend encouraging family media plans and the management of screen time in young children.



What's in a word? Qualitative and quantitative analysis of leadership language in anesthesiology resident feedback. *J Grad Med Educ* 2019; 11:44–52.

Traits frequently seen in people chosen for leadership roles, such as confidence and assertiveness (agentic descriptors), are often associated with men. Accordingly, women may face potential barriers as they seek to enter the higher levels of academic medicine. This study analyzed anesthesiology resident feedback for differences in the use of agentic descriptors based on resident sex and year. During a 1-yr period, 435 resident assessments at Stanford University School of Medicine received a qualitative content analysis of the words used during feedback and performed negative binomial regression analyses to determine significant differences in the way residents were described based on sex and training year. They found that female residents were less likely than male residents to be described as agentic after controlling for excerpt length, training year, and evaluator variability ($\beta = -0.347$; 95% CI, -0.666 to -0.028; $P = 0.033$). Senior residents were more likely to be described as agentic ($\beta = 0.702$; 95% CI, 0.402 to 1.002; $P < 0.001$) compared to junior residents. In the senior resident cohort, female residents' ratings included more descriptions of them as possessing leadership traits ($\beta = 0.704$; 95% CI, 0.084 to 1.324; $P = 0.026$). (Article Selection: Dawn Dillman. Illustration: J. P. Rathmell.)

Take home message: Female residents may be described as agentic less often than male residents in early years of training, but more agentic as they become senior residents.



Evaluation of an intervention to reduce low-value preoperative care for patients undergoing cataract surgery at a safety-net health system. *JAMA Intern Med* 2019; 179:648–57.

There are questions about the necessity of some preoperative testing that is performed in patients having cataract surgery. This study utilized a quality improvement process to review the medical records of patients scheduled for cataract surgery to identify potentially unnecessary preoperative testing. They used this information to develop guidelines for preoperative testing in patients undergoing cataract surgery. At one of two network hospitals, staff and trainees received no training or guidelines information (control group); at the second hospital, staff and trainees received guidelines and informal training

on the appropriate reduction of routine preoperative testing for patients undergoing cataract surgery (intervention group). The primary outcome was the difference in the number of preoperative medical visits, chest x-rays, laboratory tests, and electrocardiograms within 80 days of surgery between the two hospitals. Preoperative evaluations decreased from 93% to 24% in the patients in the intervention group (n = 469) but increased from 75% to 83% in the control group (n = 585, between group difference -71%; 95% CI, -86% to -65%). There were similar changes noted in the ordering of chest x-rays (between-group difference, -75%; 95% CI, -86% to -65%), laboratory tests (between-group difference, -56%; 95% CI, -64% to -48%), and electrocardiograms (between-group difference, -74%; 95% CI, -83% to -65%). (Article Selection: Martin J. London. Image: ©gettyimages.)

Take home message: This study suggests the development of guidelines to reduce potentially unnecessary preoperative testing may be associated with decreased preoperative testing and cost savings for capitated health systems.



Association between interpregnancy interval and adverse birth outcomes in women with a previous stillbirth: An international cohort study. *Lancet* 2019; 393:1527–35.

There are currently no recommendations on the optimal waiting period for conception after a stillbirth. This international cohort study investigated associations between the time interval from a stillbirth and subsequent birth outcomes. The authors included consecutive singleton pregnancies in women whose most recent pregnancy had ended in stillbirth of at least 22 weeks' gestation. Of 14,452 births included in the study, 63% of the women conceived within 12 months of the stillbirth. The median interpregnancy interval between stillbirth delivery and calculated date of conception was 9 months

(interquartile range, 4 to 19). In the entire dataset, there were 228 (2%) subsequent stillbirths, 2,532 (18%) preterm births, and 1,284 (9%) small-for-gestational-age births. For subsequent stillbirth the pooled adjusted odds ratio was 1.09 (95% CI, 0.63 to 1.91) for conception at less than 6 months and 0.90 (95% CI, 0.47 to 1.71) for conception between 6 and 11 months. Preterm birth odds ratios were 0.91 (95% CI, 0.75 to 1.11) for conception at less than 6 months and 0.91 (95% CI, 0.74 to 1.11) for conception between 6 and 11 months. Small-for-gestational-age birth odds ratios were 0.66 (95% CI, 0.51 to 0.85) for conception at less than 6 months and 0.64 (95% CI, 0.48 to 0.84) for conception between 6 and 11 months. (Article Selection: Laszlo Vutskits. Image: J. P. Rathmell.)

Take home message: This study suggests that conception within 12 months of a stillbirth is not associated with an increased risk of still birth, preterm birth, or small-for-gestational-age birth in the subsequent pregnancy.



Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: The CABANA randomized clinical trial. *JAMA* 2019; 321:1261–74.

Catheter ablation is known to restore sinus rhythm in patients with atrial fibrillation, but less clear are its effects on long-term mortality and stroke. The multinational Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) randomized trial investigated the effectiveness of catheter ablation compared to conventional medical therapy in patients with atrial fibrillation. Investigators enrolled 2,204 symptomatic atrial fibrillation patients with at least one risk factor for stroke. The catheter ablation group (n = 1,108) underwent pulmonary vein isolation. Drug therapy patients (n =

1,096) received standard medications as indicated by applicable guidelines. The primary endpoint was a composite of death, disabling stroke, serious bleeding, or cardiac arrest. During a median follow-up of 48.5 months, the primary endpoint occurred in 8.0% (n = 89) of patients in the ablation group versus 9.2% (n = 101) of patients in the drug therapy group (hazard ratio, 0.86; 95% CI, 0.65 to 1.15; P = 0.30). All-cause mortality outcomes were 5.2% ablation versus 6.1% drug therapy (hazard ratio, 0.85; 95% CI, 0.60 to 1.21; P = 0.38). Death or cardiovascular hospitalization outcomes were 51.7% ablation versus 58.1% drug therapy (hazard ratio, 0.83; 95% CI, 0.74 to 0.93; P = 0.001). Atrial fibrillation recurrence outcomes were 49.9% ablation versus 69.5% drug therapy (hazard ratio, 0.52; 95% CI, 0.45 to 0.60; P < 0.001). (Article Selection: Deborah J. Culley. Image: J. P. Rathmell.)

Take home message: For patients with atrial fibrillation, there were no differences in death, disabling stroke, serious bleeding, or cardiac arrest among patients treated with catheter ablation when compared to those treated with medical therapy.