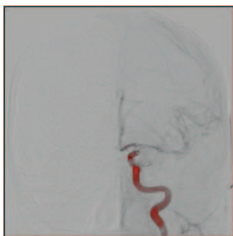


ANESTHESIOLOGY

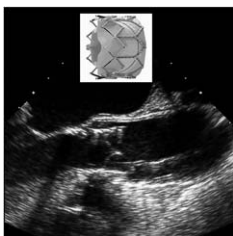


Jean Mantz, M.D., Ph.D., Editor


Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. Lancet 2016; 387:1723–31.

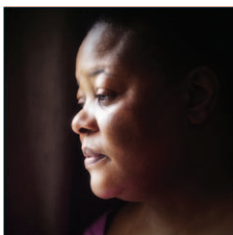
In 2015, five randomized trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis, the trial investigators aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations included. Individual data from 1,287 patients were analyzed. Endovascular thrombectomy was found to benefit most patients with acute ischemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location. (Summary: J. Mantz. Figure: Superimposed prethrombectomy (red) and postthrombectomy (black) cerebral angiography during acute stroke treatment, courtesy T. Leslie-Mazwi, Massachusetts General Hospital.)

Take home message: Endovascular thrombectomy was found to benefit most patients with acute ischemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location.


Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: A propensity score analysis. Lancet 2016; 387:2218–25.

Transcatheter aortic valve replacement (TAVR) with the SAPIEN 3 valve demonstrates good 30-day clinical outcomes in patients with severe aortic stenosis who are at intermediate risk of surgical mortality. This observational study aimed at reporting longer-term data in intermediate-risk patients given SAPIEN 3 TAVR and comparing outcomes to those of intermediate-risk patients undergoing surgical aortic valve replacement. One thousand seventy-seven intermediate-risk patients at 51 sites in the United States and Canada were assigned to receive TAVR with the SAPIEN 3 valve (952 [88%] via transfemoral access) between February and September 2014. One-year outcomes were compared with those for intermediate-risk patients treated with surgical valve replacement in the PARTNER 2A trial between December 2011 and November 2013 (963 patients), using a propensity score analysis. The primary outcome was a composite of death from any cause, all strokes, and incidence of moderate or severe aortic regurgitation. TAVR was found both noninferior (pooled weighted proportion difference of -9.2%; 90% CI, -12.4 to -6; $P < 0.0001$) and superior (-9.2%; 95% CI, -13.0 to -5.4; $P < 0.0001$) to surgical valve replacement. (Summary: J. Mantz. Image: Transesophageal echocardiogram of a deployed TAVR device with an illustration of the device (inset); transesophageal echocardiogram courtesy S. Shernan; device illustration: J. P. Rathmell.)

Take home message: TAVR might be the preferred treatment alternative to surgical valve replacement in intermediate-risk patients.


NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 2016; 533:481–6.

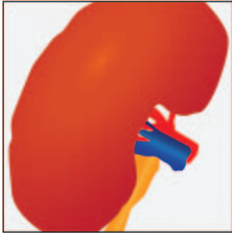
Major depressive disorder affects around 16% of the world population at some point during their lives. A growing body of evidence indicates that ketamine exerts rapid and sustained antidepressant effects after a single dose in patients with depression, but its use is associated with undesirable side effects. In this paper, the authors show by an extremely elegant combination of experimental approaches in mice that these antidepressant actions are independent of N-methyl-D-aspartate receptor (NMDAR) inhibition but involve early and sustained activation of AMPARs (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors) by the hydroxyl-norketamine metabolite. These data implicate a novel mechanism underlying the antidepressant properties of (R,S)-ketamine and have relevance for the development of next-generation, rapid-acting antidepressants. (Summary: J. Mantz. Image: © Thinkstock.)

Take home message: Ketamine, an old drug with renewed interest in anesthesia and pain, exhibits rapid-acting antidepressant effects independent of its action at N-methyl-D-aspartate receptors.


Volatile anesthetics: Is a new player emerging in critical care sedation? Am J Respir Crit Care Med 2016; 193:1202–12.

Volatile anesthetic agent use in the intensive care unit, aided by technologic advances, has become more accessible to critical care physicians. Research has demonstrated that volatile-based sedation may provide more rapid awakening and shorter time to extubation in comparison with current intravenous sedation agents (propofol and benzodiazepines). Data also indicate that volatile anesthetics exhibit organ-protective properties. However, like all sedatives, volatile agents are capable of deeply sedating patients, which can have respiratory depressant effects and reduce patient mobility. This review provides a critical analysis of current volatile anesthetic use in critical care medicine including current research, technical considerations for their use, contraindications, areas of controversy, and proposed future research topics. (Summary: J. Mantz. Image: J. P. Rathmell.)

Take home message: There might be space for the use of volatile anesthetics as alternatives to current intravenous sedation agents.



Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 2016; 375:122–33 (AKIKI multicenter randomized clinical trial). Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. JAMA 2016; 315:2190–9.

The timing of renal replacement therapy (RRT) in critically ill patients who have acute kidney injury but no potentially life-threatening complication directly related to renal failure is a subject of debate. Two major trials addressing this issue were recently published.

The first paper (AKIKI trial) was a multicenter randomized trial including 620 patients with severe acute kidney injury classification (Kidney Disease: Improving Global Outcomes [KDIGO], stage 3, stages range from 1 to 3, with higher stages indicating more severe kidney injury) who required mechanical ventilation, catecholamine infusion, or both and did not have a potentially life-threatening complication directly related to renal failure. Patients were assigned to either an early or a delayed strategy of RRT started immediately after randomization (early strategy) or if at least one of the following criteria was met (delayed strategy): severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen level higher than 112 mg/dl, or oliguria for more than 72 h after randomization. The primary outcome was overall survival at day 60. No difference was observed in the primary outcome between the two groups (60-day mortality = 48.5% [early strategy] vs. 49.7% [delayed strategy], $P = 0.79$). A delayed strategy averted the need for renal-replacement therapy in an appreciable number of patients.

The second paper (ELAIN trial) was a single-center randomized clinical trial of 231 critically ill patients with acute kidney injury. Interventions were early (within 8 h of diagnosis of KDIGO stage 2; $n = 112$) or delayed (within 12 h of stage 3 acute kidney injury or no initiation; $n = 119$) initiation of RRT. The primary endpoint was mortality at 90 days after randomization. Early initiation of RRT significantly reduced 90-day mortality (44 of 112 patients [39.3%]) compared with delayed initiation of RRT (65 of 119 patients [54.7%]) (hazard ratio, 0.66; 95% CI, 0.45 to 0.97; difference, -15.4% [95% CI, -28.1% to -2.6%]; $P = 0.03$).

The use of an intermittent (AKIKI trial) versus continuous (ELAIN trial) RRT during the first 7 days may account for, among other factors, the apparently contradictory findings of these trials on mortality. (Summary: J. Mantz. Illustration: J. P. Rathmell.)

Take home message: The beneficial effect of early versus delayed replacement therapy on mortality in critically ill patients with acute kidney injury, KDIGO classification stage 2 or 3, remains uncertain.



Detection and interpretation of shared genetic influences on 42 human traits. Nat Genet 2016; 48:709–17.

Our emerging understanding of the human genome has revealed the possibility that individual gene variants can control multiple phenotypes, although studies to date have been of limited scale. Pickrell *et al.* compared genome-wide association studies (GWAS) involving 42 traits or diseases and discovered 341 genetic loci associated with multiple traits. One example is that a variant of the ABO blood group histocompatibility gene was associated with 11 distinct traits including coronary artery disease, packed red cell volume, asthma, low-density lipoprotein levels, migraine headaches, and others. In some cases the variants in common appeared to indicate causal relationships between traits and diseases, *e.g.*, variants linked to low-density lipoprotein levels and coronary artery disease risk. In other cases the implicated genes likely played very different biological roles

in influencing the traits, *e.g.*, coronary artery disease risk and childhood ear infections. This study is of particularly high impact in that it broadens our perspectives on disease mechanisms and unexpected interrelationships. (Summary: J. D. Clark. Illustration: © Thinkstock.)

Take home message: Understanding of the human genome broadens our perspectives on disease mechanism and unexpected causal associations of genetic loci with diseases.



Unprofessional behaviors among tomorrow's physicians: Review of the literature with a focus on risk factors, temporal trends, and future directions. Acad Med 2016; 91:858–64.

Unprofessional behavior among medical students and residents is well described. These behaviors may be obvious and egregious like cheating on an exam, plagiarizing, or falsifying publications but they may also be more subtle, like falsifying Accreditation Council for Graduate Medical Education duty hours. The incidence and risk factors for these behaviors is not well described. This review evaluated 51 publications on unprofessional behavior in medical students and residents. The overall prevalence of these behaviors is 5 to 15%. Some behaviors, like falsifying duty hours, were as high as 40 to 50%. Risk factors appeared consistent across multiple studies and included stress, burnout, foreign medical training, and male gender.

Educators need to be aware of the role of stress and burnout and its potential role in propagating unprofessional behavior. Unprofessional behavior early in medical training may predict unprofessional behavior after training. Identifying and remediating these behaviors is important for our trainees, our profession, and for the public. (Summary: F. Cladis. Image: ©Thinkstock.)

Take home message: Factors favoring unprofessional behavior among residents and students include stress, burnout, foreign medical training, and male gender.