

ON THE COVER:

New scientific discoveries are emerging in the field of opioid pharmacology at the same time the United States is responding to a surge in prescription opioid misuse. "Frontiers in Opioid Pharmacology," the 2017 ANESTHESIOLOGY Journal Symposium held during the American Society of Anesthesiologists Annual Meeting, highlighted many of these new scientific discoveries. In this issue of ANESTHESIOLOGY, readers will find articles describing new original laboratory and clinical research, retrospective and population studies with practice and policy implications, and reviews on a number of topics related to the pharmacology and clinical use of opioid analgesics. Many of these are written by anesthesiologists that are leading clinician-scientists in our field. We invite you to read and learn more from the *Frontiers in Opioid Pharmacology*. Cover illustration by Sara Jarret, C.M.I.; opioid receptor illustration ©ThinkStock; Journal Symposium logo by Annemarie Johnson, Vivo Visuals.

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Frontiers in Opioid Pharmacotherapy Symposium

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D. A. Story



SPECIAL ARTICLE

- Does Aerobic Respiration Produce Carbon Dioxide or Hydrogen Ion and Bicarbonate?** 873
E. R. Swenson



The acidic end-product of aerobic metabolism is generally accepted to be carbon dioxide, but it is instead entirely possible that hydrogen ion and bicarbonate may be produced initially by the several Krebs cycle decarboxylating enzymes in the mitochondria. The greater intracellular acidosis following inhibition of carbonic anhydrase by acetazolamide is argued by two experts in acid-base physiology and function of carbonic anhydrase to support either biochemistry. In the first instance, carbonic anhydrase catalyzes bicarbonate formation to codiffuse with carbon dioxide through the cell to speed carbon dioxide elimination and prevent hypercapnic acidosis or in the second scenario to immediately speed the formation of carbon dioxide from hydrogen and bicarbonate to lower the hydrogen ion concentration.

PERIOPERATIVE MEDICINE



CLINICAL SCIENCE

-   **Opioid Abuse or Dependence Increases 30-day Readmission Rates after Major Operating Room Procedures: A National Readmissions Database Study** 880
A. Gupta, J. Nizamuddin, D. Elmofty, S. L. Nizamuddin, A. Tung, M. Minhaj, A. Mueller, J. Apfelbaum, and S. Shahul



The National Readmission Database for 2013 and 2014 was analyzed to compare readmission rates in patients with or without opioid abuse or dependence undergoing major operating room diagnostic or therapeutic procedures. Patients with opioid abuse or dependence had higher 30-day readmission rates (11.1% *vs.* 9.1%). Readmissions for infection, opioid overdose, and acute pain were more common in patients with opioid abuse or dependence. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-   **Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource Utilization: A Population-based Study** 891
S. G. Memtsoudis, J. Poeran, N. Zubizarreta, C. Cozowicz, E. E. Mörwald, E. R. Mariano, and M. Mazumdar

Using a Premier Perspective database of total hip and knee arthroplasties, patients were grouped into “opioids only” and 1, 2, or more than 2 additional modalities. There was a stepwise modality number-associated decrease in opioid patient-controlled analgesia use, opioid prescriptions, and some opioid-related side effects, but not cost of hospitalization. The strongest association was for cyclooxygenase-2 inhibitors and nonsteroidal antiinflammatory drugs. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-   **Effects of Ambient Temperature and Forced-air Warming on Intraoperative Core Temperature: A Factorial Randomized Trial** 903
L. Pei, Y. Huang, Y. Xu, Y. Zheng, X. Sang, X. Zhou, S. Li, G. Mao, E. J. Mascha, and D. I. Sessler
- Ambient operating room temperature has a negligible effect on core temperature for forced-air warmed patients, and only a small effect on unwarmed patients. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

-   **Influence of Cardiac Output on the Pharmacokinetics of Sufentanil in Anesthetized Pigs** 912
T. Birkholz, C. Leuthold, J. Schmidt, H. Ihmsen, J. Schüttler, and C. Jeleazcov





In 20 anesthetized pigs randomly assigned to have the pharmacokinetics of intravenously administered sufentanil studied under low, high, or normal cardiac output conditions, sufentanil intercompartmental clearance, compartmental volumes, and elimination clearance increased with cardiac output. As a result of cardiac output-related changes in pharmacokinetics, simulated sufentanil doses required to maintain a target plasma concentration increased with increasing cardiac output, as did its context-sensitive half-times. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- Dexmedetomidine Prevents Cognitive Decline by Enhancing Resolution of High Mobility Group Box 1 Protein–induced Inflammation through a Vagomimetic Action in Mice** 921
J. Hu, S. Vacas, X. Feng, D. Lutrin, Y. Uchida, I. K. Lai, and M. Maze



In a preclinical model, dexmedetomidine prevented cognitive deficits resulting from administration of high molecular group box 1 protein *via* both vagomimetic and humoral pathways. The results are consistent with the notion that the cognitive deficits noted after surgery or medical illness may be prevented by the administration of dexmedetomidine.

■ PAIN MEDICINE




CLINICAL SCIENCE

-   **Benefit *versus* Severe Side Effects of Opioid Analgesia: Novel Utility Functions of Probability of Analgesia and Respiratory Depression** 932
  M. Roozkrans, R. van der Schrier, L. Aarts, E. Sarton, M. van Velzen, M. Niesters, A. Dahan, and E. Olofsen

The concept of the utility function was further developed for alfentanil by calculating the probabilities of adequate analgesia with or without respiratory depression and the probabilities of inadequate analgesia with or without respiratory depression using data from three studies of 48 patients. A 50% decrease in minute ventilation was taken as the threshold for severe respiratory depression and both 25% and 50% increases in tolerated electrical current were thresholds for analgesia. The probabilities of the four conditions varied with alfentanil effect-site concentrations.

-   **Pharmacokinetic Properties of a Sufentanil Sublingual Tablet Intended to Treat Acute Pain** 943
D. M. Fisher, P. Chang, D. R. Wada, A. Dahan, and P. P. Palmer






With sublingual administration of a newly developed 30- μ g sufentanil tablet, the time to maximum plasma concentration was approximately 1 h, but the analgesic threshold was typically reached at or before 30 min, which is consistent with the onset of analgesia observed in clinical trials of the 30- μ g product. The time for the plasma concentrations to decrease below the analgesic threshold after a single 30- μ g dose was approximately 3 h, which is consistent with the duration of analgesia in those published clinical trials.

-   **New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015** 953
 G. Chai, J. Xu, J. Osterhout, M. A. Liberatore, K. L. Miller, C. Wolff, M. Cruz, P. Lurie, and G. Dal Pan

Data on new brand and generic opioid analgesic product approvals, and on retail dispensed prescription claims, were used to evaluate the opioid product space. Opioid prescriptions dispensed and amount per prescription nearly doubled, and total morphine milligram equivalents more than tripled, from 1997 to the peak in 2010, and partially declined thereafter. Generic products accounted for 68% of total opioid prescriptions in 1997 and 96% in 2015. Approval of new branded opioid products alone does not appear to be a primary driver of increased opioid prescribing.


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BASIC SCIENCE


-   **Overexpression of μ -Opioid Receptors in Peripheral Afferents, but Not in Combination with Enkephalin, Decreases Neuropathic Pain Behavior and Enhances Opioid Analgesia in Mouse** 967
A. H. Klein, H. K. Mohammad, R. Ali, B. Peper, S. P. Wilson, S. N. Raja, M. Ringkamp, and S. Sweitzer
- Using a mouse model of neuropathic pain, it was shown that increasing μ -opioid receptor expression in peripheral neurons reduced nociceptor activity and left-shifted loperamide dose-response curves. Unexpectedly, inoculation with both μ -opioid and preproenkephalin-containing herpes viruses was ineffective in reducing nerve injury–induced pain behaviors. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
-  **Buprenorphine Depresses Respiratory Variability in Obese Mice with Altered Leptin Signaling** 984
C. Angel, Z. T. Glovak, W. Alami, S. Mihalko, J. Price, Y. Jiang, H. A. Baghdoyan, and R. Lydic
- The hypothesis that sex, obesity, and leptin status modulate buprenorphine-induced changes in breathing was tested in male and female normal weight mice and in obese mice with disrupted leptin signaling. Leptin status, but not body weight or sex, contributed to the buprenorphine-induced decrease in minute ventilation variability. Mice with impaired leptin signaling had the largest buprenorphine-induced decrease in minute ventilation variability.
-   **Nonpeptide Orexin-2 Receptor Agonist Attenuates Morphine-induced Sedative Effects in Rats** 992
S. Toyama, N. Shimoyama, Y. Tagaito, H. Nagase, T. Saitoh, M. Yanagisawa, and M. Shimoyama
- In a rat model, orexin-2 receptor agonists alleviated morphine-induced decreases in locomotor activity and in sedation, which was assessed by changes in electroencephalogram. Orexin-2 receptor agonists did not attenuate the analgesic effect of morphine.

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-  **Neurologic Considerations and Complications Related to Liver Transplantation** 1008
S. S. Kumar, G. A. Mashour, and P. Picton
- Neurologic complications of surgery can be devastating. The authors review neurologic considerations and complications associated with liver transplantation and discuss strategies to prevent, identify, and treat such adverse outcomes in the perioperative period.

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-  **Abuse-deterrent Opioid Formulations** 1015
R. S. Litman, O. H. Pagán, and T. J. Cicero

The review focuses on the pharmacology of abuse-deterrent opioid formulations and discusses evidence for their use in preventing opioid overdose and addiction.

-  **Averting Opioid-induced Respiratory Depression without Affecting Analgesia** 1027
A. Dahan, R. van der Schrier, T. Smith, L. Aarts, M. van Velzen, and M. Niesters

Effective respiratory stimulants prevent opioid-induced respiratory depression without affecting the analgesic opioid response. Here the authors discuss drugs acting within the brainstem respiratory network and those acting at the carotid bodies.

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