THIS MONTH IN

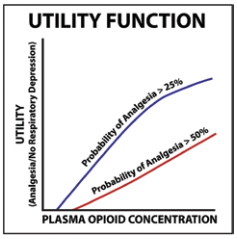
ANESTHESIOLOGY

891 Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource Utilization: A Population-based Study

The hypothesis that among total hip and knee arthroplasty recipients an increasing number of analgesic modalities used would be associated with lower opioid prescription and better perioperative complication and economic profiles was tested in a retrospective cross-sectional cohort study of 512,393 primary total hip arthroplasties and 1,028,069 primary total knee arthroplasties conducted between 2006 and 2016. Multimodal pain therapy was used in 85.6% of cases, with increased use over time of two or more additional analgesic modes. A steady decrease in postoperative opioid prescription was observed with an increasing number of analgesic modes used. Using an increasing number of modalities for pain management was associated with reduced rates of some complications commonly associated with opioids for some procedures. Small length of stay reduction with increasing number of modalities used did not translate into similar reductions in the cost of hospitalization. Cyclooxygenase-2 inhibitors and nonsteroidal antiinflammatory drugs had the strongest individual effect estimates for opioid prescription decrease. *(Summary: M. J. Avram. Image: ©ThinkStock.)*

880 Opioid Abuse or Dependence Increases 30-day Readmission Rates after Major Operating Room Procedures: A National Readmissions Database Study

The hypothesis that patients with opioid abuse or dependence would have higher readmission rates than patients without opioid abuse or dependence was tested in a retrospective cohort study using the National Readmissions Database. Of the 16,016,842 patients who had a major operating room procedure in 2013 and 2014, 94,903 (0.6%) met the definition of opioid abuse or dependence. Patients with opioid abuse or dependence had higher 30-day readmission rates (11.1% *vs.* 9.1%; odds ratio 1.26) after adjustment for potential confounders. While the most common reason for readmission in both groups was infection, infections were a more common reason for readmission in opioid abuse or dependence patients (27.0% *vs.* 18.9%). After adjustment for relevant covariates, mean hospital length of stay was longer in opioid abuse or dependence patients at both initial admission (6 *vs.* 4 days) and readmission (6 *vs.* 5 days). *(Summary: M. J. Avram. Image: ©ThinkStock.)*



932 Benefit *versus* Severe Side Effects of Opioid Analgesia: Novel Utility Functions of Probability of Analgesia and Respiratory Depression

The utility of a drug has been defined as the benefit minus the harm it produces. The utility function has been used to characterize respiratory depression relative to the analgesic effectiveness of various opioids. 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. The probability of at least 25% analgesia but less than 50% respiratory depression reaches a maximum of 0.41 at an effect-site concentration of 68 ng/ml, while for at least 50% analgesia and less than 50% respiratory depression the maximum probability of 0.21 is reached at an effect-site concentration of 93 ng/m. Maximum analgesia with serious respiratory depression peaks 10 min after a 50 μg/kg injection and optimum analgesia probability without serious respiratory depression peaks at 60 min. *See the accompanying Editorial View on* **page 867.** *(Summary: M. J. Avram. Image: Adapted from Editorial View.)*

953 New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015

Prescription trends for opioid products dispensed in the outpatient setting relative to new opioid product approvals for 1997 through 2015 were examined using nationally estimated prescription claims data and U.S. Food and Drug Administration resources to shed light on the relationship between prescribing patterns and product approvals. Dispensing of opioid analgesics increased dramatically since 1997, in both the number of prescriptions dispensed and the quantity of opioid per dispensed prescription, as measured by morphine milligram equivalents per dispensed prescription. This increase was accompanied by an increase in the market share of generic drugs, which accounted for 96% of dispensed prescriptions for opioid analgesics in 2015. The annual number of approvals, which generally increased over time, was higher in 2007 to 2015 than in 1997 to 2006. The data do not suggest a clear relationship between new product approvals and opioid utilization. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

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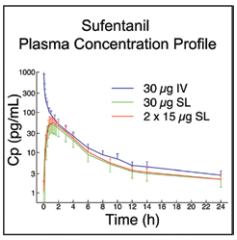
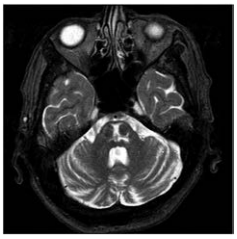


943 Pharmacokinetic Properties of a Sufentanil Sublingual Tablet Intended to Treat Acute Pain

Oral transmucosal delivery offers a noninvasive route for rapid absorption of lipophilic opioids. Available transmucosal fentanyl or buprenorphine products often contain large doses of these opioids and are not suitable for acute use in opioid-naive patients. The pharmacokinetic characteristics of newly-developed sufentanil sublingual tablets were determined using venous plasma sufentanil concentration data from four studies in healthy subjects and seven in postsurgical patients. Bioavailability of a single sublingual tablet was 52% and decreased to 35% with repeated dosing. With sublingual administration of a 30-μg 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. The time for plasma concentrations to decrease below the analgesic threshold following a single 30-μg dose was approximately 3 h, which is consistent with the duration of analgesia in clinical trials. *(Summary: M. J. Avram. Image: Adapted from original article.)*

992 Nonpeptide Orexin-2 Receptor Agonist Attenuates Morphine-induced Sedative Effects in Rats

Orexins are peptides produced by neurons in the hypothalamus. The orexin/hypocretin system plays important roles in maintaining wakefulness. Animal studies suggest the orexin type-2 receptor plays a major role in sleep/wakefulness regulation. Morphine depresses orexin neurons directly by actions on cell bodies and indirectly by presynaptic mechanisms. A study in rats determined whether the nonpeptide orexin type-2 receptor agonist YNT-185 can antagonize the sedative effects of morphine. Acute morphine administration induced short epochs of increased power and high amplitude slow-wave activity in the electroencephalogram with increases in spectral power at low and middle frequencies. Both orexin-A and YNT-185 decreased the total duration of short epochs of increased power and attenuated the electroencephalographic changes induced by morphine. YNT-185 also inhibited the decrease in locomotor activity and the increase in latency of startle response induced by morphine without attenuating its analgesic effect. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*



1008 Neurologic Considerations and Complications Related to Liver Transplantation (Clinical Focus Review)

Although outcomes after liver transplantation have improved significantly, central nervous system complications remain common and can be devastating. This review begins with a consideration of the pathophysiology of hepatic encephalopathy, which has an incidence between 30 and 45% in patients with cirrhosis and has a profoundly negative effect on patient survival, both with and without liver transplantation. Neurologic complications after liver transplantation, including seizures, osmotic demyelination syndromes, and posterior reversible encephalopathy syndrome, are then reviewed as are predictors of neurologic complications, such as infection, hepatic encephalopathy, malnutrition, renal insufficiency, and hyponatremia, to facilitate risk stratification. Monitoring options to help guide clinical care as well as prevention and treatment options aimed at improving posttransplant neurologic outcomes are then considered. Important areas identified as requiring further research include discovery of drugs to reduce the known mediators of hepatic encephalopathy and understanding impaired cerebral autoregulation in patients with end-stage liver disease. *(Summary: M. J. Avram. Image: Adapted from original article.)*

1015 Abuse-deterrent Opioid Formulations (Review Article)

The rate of fatal overdoses due to oral formulations of natural and semisynthetic opioids has risen steadily since 2000. These overdoses are the direct consequence of the use of the oral formulations in unintended ways, such as smoking, snorting, and intravenous administration. The pharmaceutical industry is increasingly developing abuse-deterrent opioid formulations that are intended to decrease intravenous and nasal abuse. The seven possible general categories of abuse-deterrent technology described by the U.S. Food and Drug Administration are reviewed, as are the three types of premarket studies and required postmarket evaluation that are part of the abuse-deterrent formulation approval process. Salient features of currently approved abuse-deterrent opioid formulations are then discussed. In considering the effectiveness of abuse-deterrent opioid formulations, the authors conclude abuse-deterrent opioid formulations will likely benefit a relatively small subset of patients and even then there is conflicting evidence as to their effectiveness in decreasing opioid abuse. *(Summary: M. J. Avram. Image: Adapted from original article.)*