Hi, this is Evan Kharasch, Editor-in-Chief of Anesthesiology, with some highlights from the May 2018 issue, as selected by the journal editors. The May 2018 issue is the Journal Symposium edition, featuring several articles whose data were first presented at the 2017 ASA Journal Symposium, Frontiers in Opioid Pharmacotherapy, sponsored by the journal Anesthesiology.

Our first article reports a database study on opioids and multimodal analgesia. Multimodal analgesia is increasingly considered routine practice in joint arthroplasties, but supportive large scale data are scarce. Dr. Stavros G. Memtsoudis of Weill Cornell Medical College, New York, and colleagues there and at Icahn School of Medicine at Mount Sinai, New York, and at Stanford University set out to determine how the number and type of analgesic modes is associated with reduced opioid prescription. They also examined complications and resource utilization. The researchers examined data from 500,000 total hip arthroplasties and 1 million total knee arthroplasties from 2006 to 2016 in the Premier Perspective database. Memtsoudis et al. divided procedures by analgesic mode, including opioids, peripheral nerve blocks, acetaminophen, steroids, gabapentin/pregabalin, NSAIDs, COX-2 inhibitors, and ketamine. They then further categorized groups into opioid only, and 1, 2, or 2+ additional modes. Multilevel models measured associations between multimodal analgesia and opioid prescriptions, and opioid-related adverse effects. Overall, 1.3 million, or 86%, of patients received multimodal analgesia. In multivariable models, with each increase in the number of modalities, there was stepwise decrease in opioid PCA use, opioid prescriptions, and some opioid-related side effects. There was however any difference in the cost of hospitalization. NSAIDs and COX-2 inhibitors were used in the majority of modalities used. While the optimal multimodal regimen is still not known, these findings encourage the combined use of multiple modalities in perioperative analgesic protocols.

The next article is another retrospective study, of patients on chronic opioids. We know that unplanned readmissions remain a significant component of the healthcare expenditure, but that the prevalence and abuse is rising. But the extent to which opioid abuse or dependence affects readmission rates and healthcare utilization is not fully understood. Dr. Atul Gupta and colleagues at the University of Chicago tested the hypothesis that surgical patients with a history of opioid abuse or dependence have higher rates of readmission and healthcare utilization. They performed a retrospective cohort analysis of patients undergoing major operating room procedures in 2013 and 2014 using the National Readmission Database. They used ICD-9 codes to identify patients with opioid abuse or dependence. The primary outcome was 30-day hospital readmission rate. Secondary outcomes included hospital length of stay and estimated hospital costs. There were 16 million patients who had a major operating room procedure whose death status was known. Of these, 95,000 had diagnosis of opioid. Patients with opioid abuse or dependence had slightly higher 30-day readmission rates of 11% versus 9% for opioid-naive patients. The most common reasons for readmission in patients with opioid abuse or dependence were infection, in 27% of patients and opioid overdose and acute pain, in 19% of patients. These findings led Gupta et al. to conclude that opioid abuse and dependence are associated with increased readmission rates and healthcare utilization after surgery.

Next we look at a proposed new method of assessing clinical opioid safety. Preclinical studies are in their infancy, and novel deterrent formulations are underappreciated by anesthesiologists. They recommend perioperative risk stratification and regular standard neurological examination. Future work targeting the use of new oral opioid technologies and COX-2 inhibitors seemed to be the most effective, plan to decrease to below the analgesic threshold following a single 30-µg dose and achieve plasma concentration was approximately 1 hour. The analgesic threshold was typically reached at or before 30 minutes, which is consistent with the onset of analgesia observed in clinical trials of the 30-µg product. The time for the plasma concentration to decrease to the most effective COX-2 inhibitor was approximately 2 hours, which was approximately 3 hours. Fisher et al. concluded that sublingual sufentanil tablets provide the opportunity to treat moderate-to-severe pain in a monitored setting non-invasively and rapidly.

Our next article reports a study opioid related sedation in animals. Sedation is a well-known and problematic side effect of opioid agonists. We also know that the opioid/hypocretin system plays an important role in maintaining wakefulness. Dr. Shoji Watanabe and colleagues of Jikei University and colleagues in Japan used a rat model to explore the potential of a non-peptide opioid receptor agonist to alleviate morphine-induced sedative effects. They used changes in electroencephalogram (EEG), locomotor activity and acoustic startle response to evaluate morphine sedative effects. They have higher risk of respiratory depression in several animal models. The authors describe the mechanisms of abuse-deterrent technology, the types of abuse-deterrent pharmaceuticals approved in the U.S. from 2011 to 2016. They assessed prescribing patterns based on dispensed prescription claims from 2007 to 2015. There were 16 million patients who had a major operating room procedure whose death status was known. Of these, 95,000 had diagnosis of opioid. Patients with opioid abuse or dependence had slightly higher 30-day readmission rates of 11% versus 9% for opioid-naive patients. The most common reasons for readmission in patients with opioid abuse or dependence were infection, in 27% of patients and opioid overdose and acute pain, in 19% of patients. These findings led Gupta et al. to conclude that opioid abuse and dependence are associated with increased readmission rates and healthcare utilization after surgery.

Our next article reports clinical studies of a new opioid delivery mechanism, oral transmucosal delivery for the rapid absorption of lipophilic opioids. Available transmucosal fentanyl or buprenorphine products are approved for use only in cancer breakthrough pain, opioid addiction treatment, or chronic pain and are not available for acute use in opioid-naïve patients. Dr. Dennis M. Fisher of the P Less Than Company in San Francisco, and colleagues at Certara Strategic Consulting, Leiden University Medical Center, and AcelRx Pharmaceuticals describe the pharmacokinetic characteristics of sublingually administered tablets containing 15 or 30 µg sufentanil. They sampled blood from 120 healthy subjects in four studies and 940 patients in seven studies. Studies in healthy subjects determined bioavailability, effect of inhibition of cytochrome P450 3A4, and the plasma concentration profile with single and hourly sublingual doses. Studies in patients evaluated effects of weight, age, sex, and organ impairment on apparent clearance. The bioavailability of a single sublingual tablet was 52%, decreasing to 55% with repeat dosing. With sublingual administration of a newly-developed 30-µg sufentanil tablet, the time to maximum plasma concentration was approximately 1 hour. The analgesic threshold was typically reached at or before 30 minutes, which is consistent with the onset of analgesia observed in clinical trials of the 30-µg product. The time for the plasma concentration to decrease to the most effective COX-2 inhibitor was approximately 2 hours, which was approximately 3 hours. Fisher et al. concluded that sublingual sufentanil tablets provide the opportunity to treat moderate-to-severe pain in a monitored setting non-invasively and rapidly.

Our next article reports a study opioid related sedation in animals. Sedation is a well-known and problematic side effect of opioid agonists. We also know that the opioid/hypocretin system plays an important role in maintaining wakefulness. Dr. Shiji Watanabe and colleagues of Jikei University and colleagues in Japan used a rat model to explore the potential of a non-peptide opioid receptor agonist to alleviate morphine-induced sedative effects. They used changes in electroencephalogram (EEG), locomotor activity and acoustic startle response to evaluate morphine sedative effects. They found that maximum effects were observed with or without YNT-185 on lomtomotor activity and on acoustic startle response. EEG analyses revealed that morphine induced high amplitude slow activity. Oxyron agonists Oxyron-A and YNT-185 attenuated these changes. Locomotor activity decreased after morphine but did not change after morphine with or without YNT-185. Startle response latency was after morphine than after morphine with or without YNT-185. These findings demonstrate the potential of opioid use in chronic pain management and the potential of these agents to alleviate analgesic effects of morphine changes and behavioral measures in rats. These results suggest that orin-2 receptor activation alleviates morphine-induced sedative effects.

Our next article addresses neurological considerations and complications related to liver transplantation. Authors Dr. Sathish S. Kumar and colleagues at the University of Michigan also discuss strategies to prevent, identify, and treat such adverse outcomes in the perioperative period. They note that outcomes after liver transplantation are related to the severity of liver disease and report on outcomes in patients with significant metabolic syndrome complications related to liver transplantation. Anesthesiologists must also evaluate interventions to mitigate and treat neurological complications within this population.

Finally, this month’s Review Article addresses abuse deterrent opioid formulations. It is written by Dr. Ronald S. Litman of Children’s Hospital of Philadelphia, and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, and colleagues at Drexel University and Washington University in St. Louis. They examine abuse-deterrent opioid formulations, which have been suggested as one way to reduce or prevent the abuse, misuse, and addiction of opioids. Numerous oral opioid formulations have received abuse-deterrent labeling by the U.S. FDA. The authors describe the mechanisms of abuse-deterrent technology, the types of premarketing studies required for FDA approval, the pharmacology of the currently approved abuse-deterrent opioid formulations, and the evidence for and against their influence on opioid use. They conclude that there is currently insufficient evidence to indicate that the availability of abuse deterrent opioid formulations has altered the trajectory of opioid use, misuse, and addiction. However, they note that interventions are in their infancy, and novel deterrent formulations are continually being developed and submitted for marketing approval.

Thank you for joining me for this brief exploration of the exciting work being published in Anesthesiology. I’ll be back in a few weeks with highlights from the June issue.

Anesthesiology. V 128 • No 5 • May 2018