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CONTINUING EDUCATION ACTIVITY

Acute Perioperative Pain Management in Total Joint Arthroplasty: Summary of Available Agents

Lopa Misra, DO

Learning Objectives/Outcomes: After participating in this CME/CNE activity, the provider should be better able to:

1. Describe the history of pain management in total joint arthroplasty and chronic persistent pain syndrome.
2. Evaluate the consequences of inadequate pain control.
3. Classify multimodal analgesia and preemptive analgesic techniques, listing the commonly used perioperative medications.
4. Identify mechanisms of pain processing.

Key Words: Central sensitization, Chronic persistent pain syndrome, Multimodal analgesia, Perioperative pain, Subanesthetic ketamine, Total joint arthroplasty

Many medications are used in acute perioperative pain management, and a complete review is beyond the scope of this article. However, 4 medications have emerged as the most commonly used and effective medications in the treatment of acute perioperative pain control: celecoxib, gabapentin, subanesthetic ketamine, and acetaminophen. This review is geared toward perioperative providers, including anesthesiologists and certified registered nurse anesthetists, surgeons, and internists involved in the perioperative care of the surgical patient.

In This Issue

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History of Pain Management in Total Joint Arthroplasty

Pain management in the early postoperative period has historically been known to be undermanaged. In the early 2000s, pain control was identified as inadequate in a large number of patients.[1] Approximately 70% of patients experienced moderate to severe pain perioperatively. Of these, almost 25% of patients experienced mild to severe adverse side effects due to the use of opioids. In 2002, reports such as these led to the formation of an American Society of Anesthesiologists Special Task Force, composed of expert academic and private practice physicians, to devise practice guidelines for acute pain management in the perioperative setting. These guidelines were updated in.

Traditionally, perioperative pain management for total joint arthroplasties included general anesthesia with opioids. General anesthesia is a known cause of postoperative pulmonary complications, postoperative nausea and vomiting, and postoperative cognitive dysfunction, among other complications. Furthermore, in many instances, use of opioids alone does not provide optimal pain control and often may predispose patients to the above-mentioned side effects. Thus, acute perioperative pain management eventually transitioned to neuraxial blocks for pain management.

Although neuraxial blocks were an improvement from the use of general anesthesia with opioids for joint surgeries, these blocks also presented their own set of complications, including severe pain as the blocks dissipated, problems with

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concurrent anticoagulation use, and falls in the postoperative period. Issues such as these resulted in moving toward using peripheral nerve blocks and multimodal analgesia for postoperative pain control with either general anesthesia or neuraxial blocks in joint surgeries.

> Suboptimal pain control in the perioperative period may lead to an increase in sympathetic tone, resulting in vasoconstriction and possibly end-organ damage.

Consequences of Inadequate Pain Control

Suboptimal pain control in the perioperative period may lead to an increase in sympathetic tone, resulting in vasoconstriction and possibly end-organ damage. Decreased gastric motility, impaired immune function, prolonged length of hospital stay, rising health care costs, and chronic persistent postoperative pain syndrome are additional consequences of inadequate pain control. Not the least of these adverse effects is an adverse perception of pain management personnel.

> How does one define when and if a chronic persistent postoperative pain syndrome has developed?

Elderly patients are especially at risk due to adverse effects from escalating doses of opioids, including a greater propensity for respiratory depression postoperatively, hypotension, dizziness, confusion, and delirium. A final consequence may be development of a chronic persistent postoperative pain syndrome.

But how does one define when and if a chronic persistent postoperative pain syndrome has developed? Many criteria must be included, such as the degree of pain postsurgery, preexisting pain conditions and their impact on quality of life, the development of pain that lasts at least 2 months with signs and symptoms of chronic neuropathic pain. Other causes of pain such as cancer and infection must be excluded.[3]

Furthermore, certain factors may predispose patients to develop chronic persistent postoperative pain syndrome. These factors are divided into 3 main categories and include preoperative factors, surgical factors, and postoperative factors. Preoperative factors include preexisting pain, repeat surgery, psychological vulnerability, and work-related injuries. Surgical factors are listed as the type of surgery, surgical approach, and risk of nerve injury due to surgery. Lastly, postoperative factors include the severity of early postoperative pain, the need for postoperative radiation or chemotherapy, and neuroticism or psychologic vulnerability.

Thus, issues such as these have led to the popularity of increasing the use of nonopioid medications for perioperative pain control as part of the multimodal approach to pain control. Because treatment of chronic persistent pain syndrome is challenging, use of multimodal and pre-emptive analgesia perioperatively is crucial. Several opioid alternative medications are currently used, including cyclooxygenase-2 (COX-2) inhibitors, gabapentin, acetaminophen, and subanesthetic ketamine. Part of the plan for postoperative pain management must also include multimodal analgesic techniques and preemptive pain plans.

Multimodal Analgesia

Multimodal analgesia modulates various pain pathways while simultaneously decreasing unwanted side effects and providing optimal pain relief.[4] Adverse side effects of opioids include nausea, vomiting, sedation, ileus, respiratory depression, and itching. Opioid-alternative medications are administered in the preoperative period and continued throughout the perioperative period, thereby becoming an integral part of preemptive analgesia.

As the name implies, preemptive analgesia begins before the start of surgery. It aids in preventing both peripheral and central nervous system nociceptors sensitization by preventing the production of inflammatory neurotransmitters. The rationale implies that sensitization of nerve fibers lowers pain threshold, resulting in hypersensitivity to external stimuli in the perioperative period and the development of chronic neuropathic pain. By blocking this pathway, anesthesia and pain providers can improve the overall analgesia experience for the patient, resulting in improved outcomes and decreased incidence of development of chronic neuropathic pain.

Mechanism of Pain Processing

There are 4 main sites of pain processing: peripheral nociceptor (nerve endings), nerve and dorsal root ganglion, the dorsal horn of the spinal cord, and the brain and brainstem[5] (Figure 1). Drugs act at several sites along this pathway.

How Each Medication Contributes to Pain Management

Cyclooxygenase-2 Inhibitors

Multimodal analgesia has been gaining popularity over the past several years. A variety of medications are used, one of which includes COX-2 inhibitors, which reduce pain and inflammation, as do other nonsteroidal anti-inflammatory drugs (NSAIDs). COX-2 inhibitors have been championed

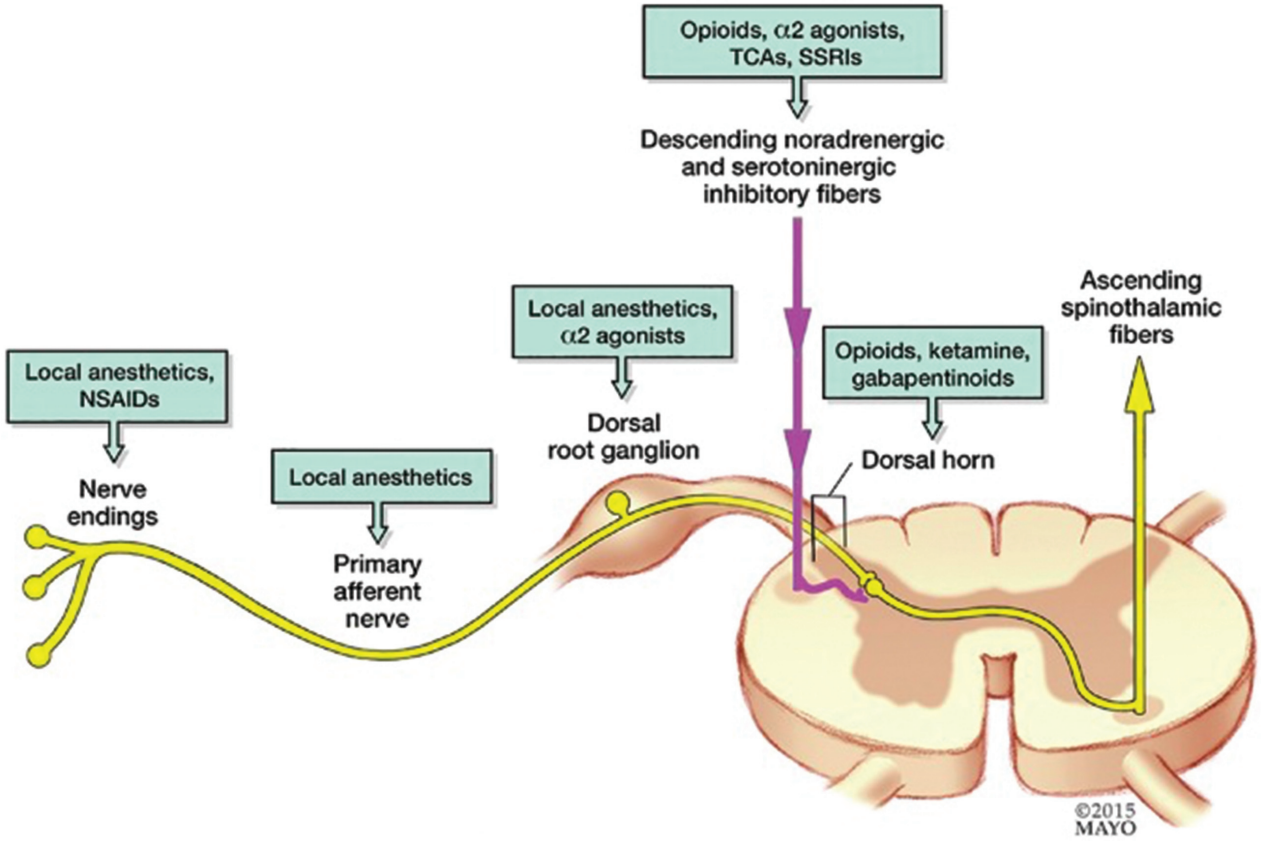

Figure 1. The several sites along the pain pathway are indicated and the sites at which different drugs act. A variety of drugs acts at various anatomic locations along the pain-signaling pathway. Ketamine modulates pain at the dorsal horn of the spinal cord.

over COX-1 inhibitors because of the favorable side effect profile. COX-2 inhibitors work peripherally and prevent prostaglandin production. They have a decreased risk of gastric ulcers, decreased risk of platelet dysfunction, and decreased risk of renal injury compared with COX-1 inhibitors/NSAIDs.[4] However, some COX-1 inhibitors such as Arthrotec (diclofenac and misoprostol) have been used successfully in the perioperative period with minimal adverse side effects. And although there has been concern regarding cardiovascular complications associated with COX-2 inhibitors, doses of up to 400 mg per day have not been shown to produce adverse cardiovascular effects.

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Multiple studies have supported their use, including large meta-analyses. One such study of 8 randomized controlled trials included 571 patients undergoing total knee replacement. The patients received COX-2 inhibitors preoperatively. Results showed lower pain scores per visual analogue scales (VAS), improved range of motion, less opioid consumption, and decreased opioid adverse effects in up to 3 days postoperatively, as compared with those patients who did not receive COX-2 inhibitors preoperatively.[6]

In another randomized, double-blind, placebo-controlled study of 107 patients undergoing total knee arthroplasty, patients were given 200 mg of celecoxib twice a day for 6 weeks postoperatively. Results indicated a decrease in the number of narcotic pill consumption in the celecoxib group (76.3 ± 55 vs 138 ± 117) ($P = 0.003$).[6] VAS pain scores were also lower at 3, 6, and 12 weeks postoperatively in the celecoxib group. Furthermore, a greater degree of knee flexion was noted in the celecoxib group up to 1 year postoperatively as measured by the American Knee Society Scores and the Oxford Knee Score scales used at 3 and 6 weeks postoperatively. The American Knee Society Score describes patients' functional outcomes before and after total knee arthroplasty. It assigns a number to pain score, alignment, and contracture. The Oxford

Knee Score scale is the United Kingdom's version of the American Knee Society Score.

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Gabapentinoids

Gabapentin has also been proven to be beneficial when used as part of multimodal analgesia perioperatively. Although gabapentin has a structure similar to γ-aminobutyric acid, it does not act on this receptor. Instead, it works by decreasing stimulus-induced hyperexcitability of the posterior horn neurons. Gabapentinoids also possess an antihyperalgesic effect via postsynaptic binding of gabapentin to the α 2-δ subunit of the dorsal horn-neuron voltage-gated calcium channels. A resulting decrease in calcium entry into nerve endings leads to decreased neurotransmitter release.[7]

Gabapentin was initially used as an antiepileptic for partial seizures in the 1990s. However, since then, multiple studies have shown its efficacy in a variety of other settings, including the perioperative setting.

In 1 study, gabapentin was administered 1.2 g per day 1 hour before coronary artery bypass graft surgery and continued 2 days postoperatively.[8] Results showed that postoperative pain scores at days 1, 2, and 3 were significantly lower in the gabapentin group than in the placebo group. Other studies have indicated its benefits in orthopedic surgeries. Significantly lower pain scores were obtained at 2 hours postoperatively in patients who received preemptive gabapentin undergoing internal fixation of the tibia under spinal block.[9]

Yet another study examined the effects of gabapentin on acute postoperative pain and morphine intake in patients undergoing spine surgery.[10] Gabapentin 1200 mg given 1 hour before incision resulted in lower pain scores at 1, 2, and 4 hours postoperatively. In addition, morphine consumption was lower in the gabapentin group than in the placebo group, leading to the added benefit of lower incidence of postoperative nausea and vomiting because of opioids.[10]

It is important to note that abrupt cessation of gabapentin may result in withdrawal symptoms similar to those seen in alcohol withdrawal, including irritability, agitation, anxiety, palpitations, and diaphoresis within 24 to 48 hours.[8]

Pregabalin has also been known to provide excellent analgesia when used as part of a multimodal analgesia plan in lieu of gabapentin. Although it is more potent than gabapentin and can reach optimal cerebrospinal fluid levels faster than gabapentin, cost remains an issue with pregabalin. Thus, gabapentin is used more commonly in perioperative pain management.

Acetaminophen

Use of acetaminophen as part of multimodal analgesia has been on the rise for the past few years. This drug has been in use for more than 100 years as an analgesic and an antipyretic. Studies over the past decade have confirmed its efficacy as a pain reliever in the perioperative period while simultaneously allowing the decrease in the amount of opioids consumed and the risk of adverse side effects of opioids.[11] The IV form of acetaminophen has been used in Europe since 2002. However, it was not introduced into the United States until January 2011. Although the mechanism of action is not completely understood, acetaminophen is thought to work via centrally mediated pathways. It is also thought to be a cannabinoid receptor agonist, COX-2 isoenzyme inhibitor, and an agonist of the transient receptor potential cation channel, subfamily V, member 1, a central antinociceptor.[11]

A major benefit of acetaminophen is that 1000 mg of IV acetaminophen has been shown to be as effective as morphine 10 mg given intravenously. Its use is favored over the oral and rectal routes because the IV form reaches peak cerebrospinal fluid concentration quickly. In addition, IV acetaminophen has been used effectively in all phases of the perioperative period and is not dependent on delayed absorption, which is noted in oral administration.

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Pharmacokinetics demonstrate that serum therapeutic levels of acetaminophen needed for optimal effect are 16 and 10 μg/mL in adults and children respectively.[11] When given intravenously, analgesic effects are achieved within 15 minutes of administration, with the peak effect reached within 1 hour. The duration of effect lasts approximately 4 to 6 hours. Although time to reach peak effect with the IV formulation is approximately 15 minutes, it requires 45 to 75 minutes to reach peak effect when given orally. Time to reach peak effect is even longer if acetaminophen is

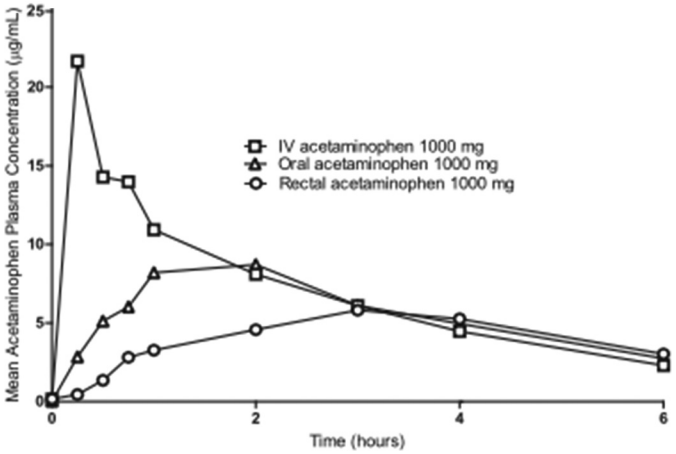

Figure 2. Mean plasma acetaminophen concentration-time curves after IV, oral, and per rectum administration of 1000 mg (n = 7 for oral; n = 6 for IV/per rectum). (Reprinted with permission from *Pain Pract*. 2012;(12):523-532.)

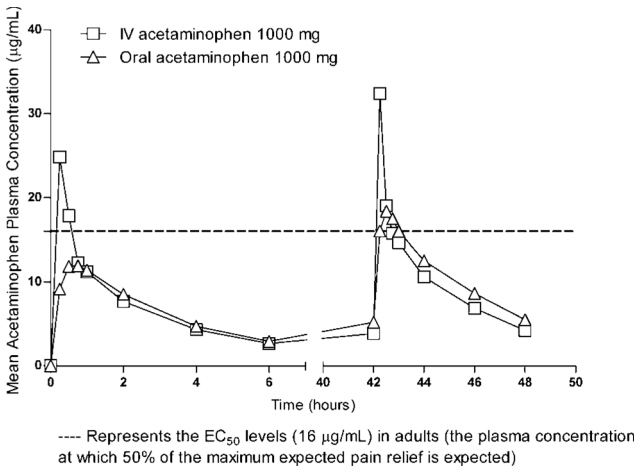

Figure 4. The EC_{50} levels (16 µg/mL) in adults (the plasma concentration at which 50% of the maximum expected pain relief is expected). (Reprinted with permission from *Pain Pract*. 2012;(12):523-532.)

administered rectally. The median time to reach maximum plasma concentration (or T_{max}) for rectal administration is 3 to 4 hours. Advantages of the IV route as compared with the oral and rectal routes are shown in Figures 2 to 4.

Multiple studies have shown evidence to support the use of acetaminophen in the perioperative period as part of a multimodal analgesia regimen. Not only does it provide effective perioperative pain control, it also allows providers to decrease the amount of opioids needed in the perioperative period, thereby reducing the adverse side effects of the opioids.

Ketamine

Ketamine has recently gained popularity as part of a multimodal analgesia regimen. Use has been on the rise in the perioperative period for several reasons. It is a phencyclidine derivative, which was initially referred to as CI-581. Ketamine was initially used as an anesthetic agent in the early 1960s with its first documented use in the late 1960s.[12] It has traditionally been used as an induction agent in hemodynamically unstable patients; however, over the past few years, research has supported its use in the perioperative period because of its ability to prevent chronic pain.

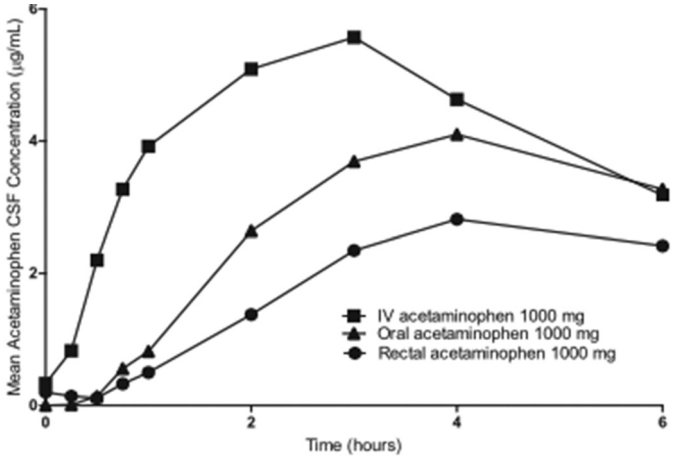

Figure 3. Mean cerebrospinal fluid acetaminophen concentration-time curves after IV, oral, and per rectum administration of 1000 mg. (Reprinted with permission from *Pain Pract*. 2012;(12):523-532.)

Ketamine has multiple street names, including Special K, vitamin K, and Kit Kat, to name a few. It exerts its action via the *N*-methyl-D-aspartate (NMDA) receptor. It is an NMDA receptor antagonist, and at anesthetic doses, leads to multiple central nervous system effects resulting in a dissociative state.

> Although there has been concern regarding side effects with the use of subanesthetic ketamine, most of these have been mild and well tolerated.

In addition, at subanesthetic doses ketamine possesses centrally mediated analgesic effects, and therefore plays an important role in pain processing. Anesthetic dose is 1.0 mg/kg or more intravenously. Subanesthetic dosing for ketamine is 0.3 mg/kg or less intravenously. The NMDA receptor works primarily in the dorsal horn of the spinal cord. The steps leading up to central sensitization are as follows: tissue injury → glutamate release in dorsal horn → glutamate binds to NMDA receptors → NMDA receptors activated → intracellular processes activated → resulting in altered behavior → central sensitization. The end result is chronic pain.

Central sensitization is also referred to as "wind-up" phenomena (Figure 5).

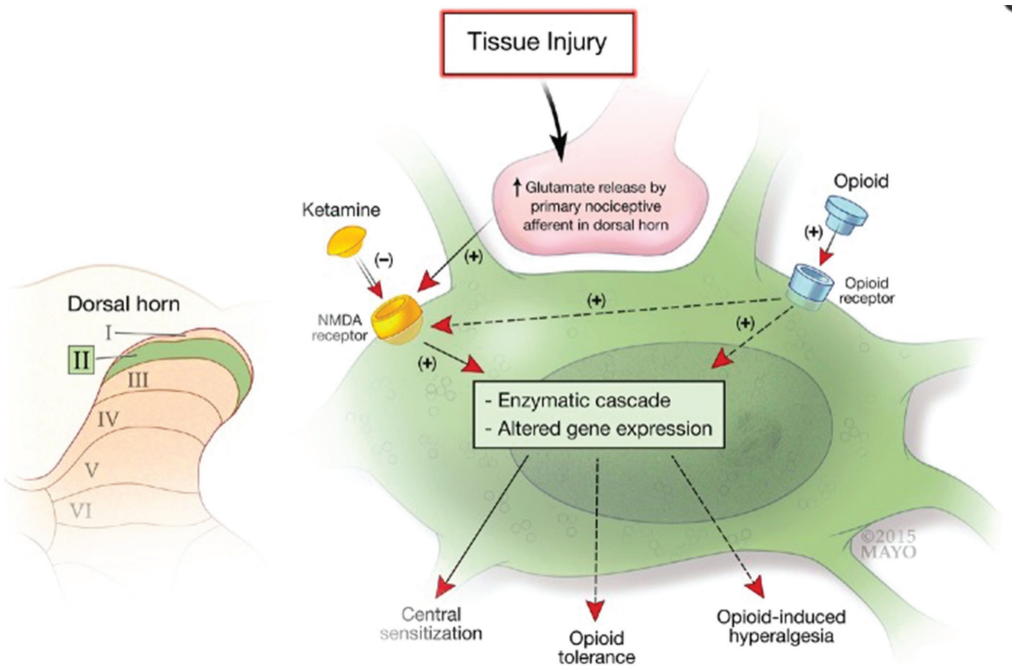

Figure 5. Site and mode of action of ketamine. The activated primary nociceptive afferent from the periphery releases glutamate at the second-order sensory neuron in the dorsal horn of the spinal cord. The glutamate binds to NMDA receptors. Ketamine blocks the NMDA receptor, which attenuates the development of central sensitization and opioid tolerance and hyperalgesia. Reprinted with permission from Mayo Clinic, Phoenix, Arizona.

Although there has been concern regarding side effects with the use of subanesthetic ketamine, most of these have been mild and well tolerated by patients. The drug is associated with a low incidence of mild psychomimetic symptoms, nystagmus, and double vision when administered in subanesthetic doses. However, there are some contraindications to its use because of its metabolism. Therefore, the clinician may choose to avoid its use in patients with renal or hepatic insufficiency.

> Subanesthetic ketamine has been used successfully in painful procedures, opioid-tolerant patients, those with opioid-induced hyperalgesia, surgery with high risk of developing chronic postsurgical pain syndrome, and any time there is a desire or need to minimize the use of perioperative opioids.

Specific medical conditions where subanesthetic ketamine is not suitable include high-risk coronary artery or vascular disease, uncontrolled hypertension, increased intracranial and intraocular pressure, psychosis, sympathomimetic syndrome, recent liver transplantation, porphyria, and globe injuries. Subanesthetic ketamine has been used successfully in painful procedures, opioid-tolerant patients, those with opioid-induced hyperalgesia, surgery with high risk of developing chronic postsurgical pain syndrome, and any time there is a desire or need to minimize the use of perioperative opioids.

Multiple studies have supported the use of ketamine in perioperative multimodal analgesia. For example, the authors of a systematic review of 70 studies in which IV perioperative ketamine was given concluded that IV ketamine significantly decreased postoperative opioid needs, and also increased the time to the first operative narcotic requirement.[5]

Yet another such study included 101 patients and reported a 37% decrease in morphine use over a 48-hour period in opioid-tolerant patients undergoing spine surgery.[13]

Furthermore, a meta-analysis of 14 studies compared 2 groups of patients.[14] One group acted as placebo control and the other group received perioperative IV ketamine. Results demonstrated that subanesthetic doses of ketamine resulted in a 25% and 30% decrease in risk of persistent postsurgical pain at 3 and 6 months, respectively. Promising results such as these have given way to protocols in place for use of perioperative ketamine and continuing a

subanesthetic infusion for 48 hours postoperatively with excellent outcomes. In fact, centers such as the University of Pittsburgh Medical Center and Mayo Clinic in Florida and Arizona have also begun implementing such practices.

The question of appropriate dosing of subanesthetic ketamine in perioperative pain management is still controversial, however. Although there are no set recommendations in regard to dosing of ketamine, most experts advocate injecting a bolus of ketamine at induction, followed by serial doses or, in some cases, an infusion.

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Extensive research on the ideal timing and dosing of ketamine has been conducted.[15] Recommendations conclude that ketamine should be dosed preincision as a bolus, and then followed by either an infusion or serial boluses. Indeed, ketamine use in the perioperative period has been shown to be an effective way of decreasing narcotic needs and side effects associated with their use, while also decreasing the risk of chronic pain.

Conclusion

Evidence supports the use of multimodal analgesia in the perioperative period. Multiple modalities are employed in this technique, including regional blocks, periarticular injections, and a variety of nonopioid medications, with excellent results including shorter length of hospital stay, reduced number of adverse side effects, and improved patient satisfaction. Medications should be dosed 1 to 2 hours before surgery in the preoperative period and continued for 48 to 72 hours postoperatively.

Dosing recommendations are as follows:

- Celecoxib: 200 mg orally.
- Gabapentin: 300 mg orally.
- Acetaminophen: 1000 mg IV or orally.
- Ketamine: 15 to 20 mg IV bolus with induction of anesthesia followed by serial boluses or infusion for 24 hours.

All 4 of the above-listed medications are administered preoperatively in the recommended doses (in no preferential order) as part of a multimodal analgesia strategy for total joint procedures. ■

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Medical Marijuana Issue Complicated by Scientific, Political, And Regulatory Uncertainties

Anne Haddad

A scientific panel discussion and multi-faceted look at cannabinoids in pain management was one of the more well-attended sessions at the New York State Society of Anesthesiologists' Post-Graduate Assembly (PGA) in December 2016. As of the end of 2016, state legislatures in just over half of the United States had approved at least some form of marijuana use for medical purposes with a physician's prescription, and a handful more were expected to consider such laws during 2017.

Will DEA Registration Put Opioid Prescribers At Risk?

For pain physicians who are registered with the US Drug Enforcement Administration to prescribe controlled substances, however, there is still a pressing concern: Even if they prescribe medical marijuana in a state that allows it, their DEA registration is a federal status. Will they be vulnerable to sanctions by the US DEA? Even if prescribing marijuana makes them more vulnerable to *investigation* by the DEA, it can have a chilling effect.

Under federal law, there is no such thing as medical marijuana—there is only marijuana, a Schedule I substance, meaning it is addictive and serves no medical purpose in the eyes of federal law.

Although at least 26 states have passed laws allowing physicians to prescribe marijuana for certain patients, marijuana remains illegal in federal court. There have been challenges to this in the past, mostly during President George W. Bush's administration. President Barack Obama's administration did not prosecute medical marijuana cases that did not violate the state laws where they exist.

For the cases that came to the US Supreme Court during the Bush years, however, the court ruled against any attempts to legalize medical marijuana.

Know the Science and the Law—Even if You Don't Prescribe

Whether or not a physician is willing to prescribe marijuana, all pain practitioners should become aware of the medical and scientific research behind these substances, their interaction with traditional prescription and over-the-counter drugs, and their potential long-term side measurable effects on the human brain, said experts on the scientific panel in New York in December.

Presenting the body of evidence on cannabinoids were:

- Sudhir Diwan, MD, DABIPP, clinical associate professor at Albert Einstein College of Medicine and executive director of Manhattan Spine & Pain Medicine, who focused on literature related to cannabinoids and chronic pain.
- Oscar DeLeon Casasola, MD, professor and chief of pain medicine at Roswell Park Cancer Institute and professor and vice-chair for clinical affairs in the Department of Anesthesiology at the Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, who focused on literature indicating some long-term effects on the brain from use of marijuana.

Diwan gave an overview of existing literature, but he emphasized that there is still a shortage of high-quality controlled and randomized studies on medical marijuana. Still, he said, in states where it is legal, pain practices are bound to see patients who have been or could still be using medical marijuana or self-medicating with it.

Pain Practitioners Must Learn About Cannabinoids

"You should at least learn as much as you can about it," Diwan told those present, who attended from all over the country and abroad. Considering the disastrous way in which opioid prescribing led to an unintended rise in deaths from overdose and abuse before the medical community fully understood the risks, he said, practitioners owe it to their patients to proactively learn as much as they can about a drug that may see increased prescribing and use in the next several years.

"The legalization of marijuana use, recreational and/or medical, has almost forced us to learn everything about marijuana," Diwan said. "Does it have analgesic effects? Is it safe? How would affect the prescriptions of opioids? Urine toxicology screen with positive marijuana: Now what? Would you discharge the patient from practice? What about concurrent use of opioids? Do we have enough knowledge of interactions?"

Diwan told the group that use of marijuana for headache and back pain has been documented as early as the 6th Century, with references in the medical literature since the mid-1800s. However, it was removed from medical use in the 1940s because of increased scrutinization over psychoactive and recreational use.

Much of the science behind medical marijuana has been to find ways to maximize the therapeutic benefits while removing the psychoactive properties that make it more appealing for recreational use and more addictive.

Two Main Cannabinoids Being Studied

The marijuana plant actually contains more than 113 identified cannabinoids. Of these, tetrahydrocannabinol (THC) is responsible for the psychoactive properties, while cannabidiol (CBD) has been shown to have medical application, but without the psychoactive properties.

Diwan wrote in his presentation abstract: "The THC has psychoactive, anti-inflammatory, neuro-protective, antinausea, and analgesic actions. The CBD is non-psychoactive, with no significant affinity for CB1 and CB2 receptors. It blocks formation of 11-OH-THC (the most psychoactive metabolite of THC). It is a potent CYP450 3A1 inhibitor and mitigates the side effects of THC (anxiety, dysphoria, panic reactions, and paranoia) while improving THC's therapeutic activity."

New York State Law on Medical Marijuana

Sudhir Diwan, MD, recently shared with colleagues an example of how medical marijuana is regulated in New York, where a state law allowing medical prescribing of marijuana expanded to include severe or chronic pain as a qualifying condition, as of December 1, 2016.

The law in New York requires physicians to take an online course to become certified by and registered with the state. The prescriber chooses the route of delivery appropriate for each patient, choosing from inhalation, sublingual, oral, or topical forms. The pharmacies/dispensaries specialize in certain formulas and ratios of tetrahydrocannabinol (THC) to cannabidiol (CBD).

The pharmacies and physicians exchange documentation, but once a patient is registered, he or she receives a card and can receive the prescription directly from the dispensary.

New York allows these certified practitioners to prescribe marijuana for conditions that include:

- Cancer
- AIDS or HIV-positive status
- Amyotrophic lateral sclerosis
- Parkinson disease
- Multiple sclerosis
- Spinal cord injury with intractable spasticity
- Epilepsy
- Inflammatory bowel disease
- Huntington disease
- Neuropathies
- Severe debilitating or life-threatening conditions clinically associated with:
  - Cachexia (wasting syndrome)
  - Severe nausea
  - Seizures with severe or persistent muscle spasms
- Severe or chronic pain

Source: Sudhir Diwan, MD

Brain Studies Indicate Risk with Long-Term Marijuana Use

While Diwan focused his presentation on some of the potential benefits that medical marijuana may provide for chronic pain patients, DeLeon presented data from studies that have found evidence that marijuana may negatively affect function even if it does provide some relief from pain. Physicians, he said, will need to be vigilant about considering the drug's effect on function in order to help patients weigh the risks versus the benefits.

DeLeon's talk was entitled, "Would You Use Marijuana If You Knew This?"

"This is an important question, because with the approval of marijuana use, we may be facing another addiction epidemic," DeLeon said.

His data included studies showing incentive-sensitization models that suggest that alterations in the brain's reward system are, at least in part, related to cannabinoid use. Data have shown sensitization of mesocorticolimbic regions and disruption of natural reward processes after marijuana use. These pathways play a central role in addiction.

DeLeon presented data from studies showing changes in both the gray and white matter brain structure. Adolescents are particularly vulnerable, the data show, demonstrating more deficits in effortful processing and complex cognition.

He also referred to studies indicating marijuana's anti-inflammatory and antioxidant properties may also lead to neural changes, including greater myelination and possible neurotoxicity.

"Whether abstinence reverses such effects remains unknown," DeLeon said. ■

Further Reading

Articles Diwan cited in his abstract include:

Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther*. 2011;90:844-851.

Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systemic review and meta-analysis. *JAMA*. 2015;13(24):2456-2473.

Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare Part D. *Health Affairs*. 2016;35(7):1230-1236.

Articles DeLeon cited in his presentation include:

Filbey FM, Aslan S, Calhoun VD, et al. Long-term effects of marijuana use on the brain. *Proc Natl Acad Sci USA*. 2014;111:16913-16918.

Nestler EJ. Molecular basis of long-term plasticity underlying addiction. *Nature Rev Neurosci*. 2001;2:119-128. Erratum in *Nat Rev Neurosci*. 2001 Mar;2(3):215.

Topics in Pain Management CE Quiz

To earn CME credit using the enclosed form, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **January 31, 2018**. Only two entries will be considered for credit.

Online CME quiz instructions: Go to **http://cme.lww.com** and click on "Newsletters," then select *Topics in Pain Management*. Enter your ***username*** and ***password.*** First-time users must register. After log-in, follow the instructions on the quiz site. You may print your official certificate ***immediately.*** **Please note:** Lippincott CME Institute, Inc., ***will not*** mail certificates to online participants. **Online quizzes expire on the due date.**

To earn nursing CNE credit, you must take the quiz online. Go to **www.nursingcenter.com**, click on CE Connection on the toolbar at the top, and select Browse by Journal. On the next page, select *Topics in Pain Management.*

Log-in (upper right hand corner) to enter your ***username*** and ***password.*** First-time users must register. After log-in, locate and click on the CE activity you are interested in. There is only one correct answer for each question. A passing score for this test is 7 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost. For questions, contact Lippincott Williams & Wilkins: 1-800-787-8985. The registration deadline for CNE credit is **February 28, 2019**.

1. **A 46-year-old man presents for left total shoulder arthroplasty. The patient has vague abdominal pain and a history of porphyria. Appropriate multimodal analgesia options include all of the following *except***
   A. interscalene nerve block
   B. IV acetaminophen 1000 mg
   C. celecoxib 200 mg orally
   D. IV ketamine followed by an infusion
2. **All of the following are possible mechanisms of action for acetaminophen *except***
   A. COX-2 isoenzyme inhibitor
   B. cannabinoid receptor agonist
   C. agonist of transient receptor potential anion channel
   D. centrally mediated pathways
3. **A 56-year-old woman presents for laparoscopic cholecystectomy. A few minutes before proceeding to the operating room, the patient becomes agitated and begins to sweat profusely. Her current medications include a β-blocker for treatment of hypertension and a "nerve pill" that she has forgotten to take for past 2 to 3 days. The *most* likely reason she is agitated and sweating is**
   A. withdrawal symptoms from cessation of β-blocker
   B. alcohol withdrawal
   C. anxiety
   D. withdrawal from gabapentin from abrupt discontinuation
4. **A 1000 mg dose of IV acetaminophen affords equivalent analgesia to**
   A. fentanyl 25 μg
   B. celecoxib 400 mg
   C. morphine 10 mg
   D. ketamine 20 mg
5. **Ketamine 1 mg/kg helps prevent central sensitization and chronic pain by which one of the following mechanism of action?**
   A. Opioid receptor agonist
   B. COX-2 isoenzyme inhibition
   C. NMDA receptor antagonism
   D. Peripherally mediated pathways
6. **Which one of the following statements is *true*?**
   A. Gabapentin and pregabalin are equipotent.
   B. Gabapentin acts on the γ-aminobutyric acid receptor.
   C. Pregabalin has a faster onset of action than gabapentin.
   D. Gabapentin reduces sodium entry into nerve endings.
7. **Which of the following is a pain processing site?**
   A. Peripheral nociceptor
   B. Nerve endings
   C. Dorsal root ganglion and dorsal horn of the spinal cord
   D. All of the above
8. **A 36-year-old man with chronic pain, alcohol overuse, and a spinal cord stimulator in place presents to the operating room for a total ankle arthroplasty. Optimal perioperative pain management includes all of the following *except***
   A. regional block including neuraxial or peripheral nerve block
   B. high-dose opioid technique
   C. COX-2 enzyme inhibitors
   D. pregabalin
9. **A 76-year-old man with acute bowel obstruction, sepsis, and free air was taken emergently to the operating room. His medical history includes an echocardiogram showing an ejection fraction of 33% due to a history of cardiomyopathy. Which of the following is/are contraindicated in this patient?**
   A. IV acetaminophen
   B. Induction dose of ketamine
   C. Low-dose opioids
   D. All of the above
10. **Characteristics of gabapentin include all of the following *except***
    A. Acts on the voltage-gated calcium channels in the central nervous system
    B. Effective as part of a multimodal analgesic regimen
    C. Absence of withdrawal symptoms following cessation
    D. Initially used as an antiepileptic for partial seizures

ICYMI: IN CASE YOU MISSED IT

Notes from recent studies related to pain management, compiled by Elizabeth A. M. Frost, MD.

Pain and Sex Hormones: A Review of Current Understanding

Many studies have demonstrated sex-specific differences in pain sensitivity and pain threshold, but the underlying mechanisms remain unknown. Gonadal hormones may influence nociceptive processing. In this review article, the authors present the data and identify the many functions of gonadal hormones on several chronic pain conditions including migraine, tension headache, fibromyalgia, temporomandibular syndrome, rheumatoid arthritis, and back pain. An attempt is made to draw conclusions. (*See* Maurer AJ, Lissounov A, Knezevic I, et al. Pain and sex hormones: a review of current understanding. *Pain Manag*. 2016;6(3):285-296. doi:10.2217/pmt-2015-0002.PMID:26983893.)

Hormones in Pain Modulation And Their Clinical Implications For Pain Control: A Critical Review

The authors present an overview of many studies in an attempt to determine whether the relationship between the perception of pain and hormones is causative and how these processes interrelate. They note that the relationship between pain perception and endocrine effects suggests that hormone assays might be used as biomarkers of chronic pain syndromes and could be developed as therapeutic agents. (*See* Chen X, Zhang J, Wang X. Hormones in pain modulation and their clinical implications for pain control: a critical review. *Hormones (Athens)*. 2016;15(3):313-320. doi:10.14310/horm.2002.1696.)

Sex Differences in the Epidemiology, Clinical Features, and Pathophysiology Of Migraine

The authors note that migraine is 2 to 3 times more prevalent with longer duration, increased risk of recurrence, and greater disability in women than in men. Several comorbidities have been identified in both sexes including asthma, anxiety, depression, and other chronic pain conditions. Migraine associated with an aura is a risk factor for vascular disease in women, but because of a paucity of data, the same relationship has not been determined in men. The conclusions drawn are that migraine is underdiagnosed in men, causing suboptimal treatment and less participation of men in trials. (*See* Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol*. 2016; pii:S1474-4422(16)30293-9. doi:10.1016/S1474-4422(16)30293-9.)

Coming Soon:

- Enhanced Recovery Programs and Pain Management
- Biopsychosocial Contributors to Adolescent Chronic Pain: What Health Care Providers Should Consider Regarding Social Influences in their Evaluation and Treatment