13 Pain Management in Unicompartmental Knee Arthroplasty

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Clinical Case

A 56-year-old woman presents for evaluation of left knee pain. She reports that her left knee pain has been prevsent for several years, worsening of late, does not radiate, and is a 9/10 on a visual analog scale, worse with ambulation and weight bearing. She has a medical history of obesity, fibromyalgia, depression, and hypertension. Surgical history is remarkable for tonsillectomy and lumbar microdiscectomy. Medications include hydrochlorothiazide 25 mg QD, duloxetine 30 mg QD, naproxen 500 mg BID, and oxycodone 10 mg TID for the past 6 months. Allergies include hydrocodone and iodinated contrast. Social history is negative for substance abuse, and review of systems is unremarkable. Examination is consistent with exquisite pain to palpation over the medial aspect of the left knee. There is no numbness, dysesthesias, or allodynia. Radiographs confirm findings of advanced osteoarthritis of the medial compartment of the left knee. She is consented for left UKA.

- What are the risk factors for this patient having poorly controlled postoperative pain?
- What can be done preoperatively to optimize this patient from a pain perspective?
- What would be an appropriate anesthetic plan?
- How does one successfully manage opioids prescribed after surgery?
- If this patient develops chronic pain, what is the next course of action?

Introduction

Pain remains a limiting factor in recovery from surgery despite numerous advances in surgical and anesthetic techniques. Unicompartmental knee arthroplasty (UKA) requires the development of an optimal pathway to allow patients to mobilize early and with as little pain as possible. In order to obtain long-term success rates, proper patient selection and application of anesthetic and analgesic techniques is prudent. This chapter is intended to enhance the reader's ability to recognize and optimize risk factors for the development of persistent pain after UKA, understand the anesthetic options for UKA, and appreciate the molecular basis of the pharmacologic agents to treat postoperative pain in these patients.

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T. L. Gerlinger (ed.), *Unicompartmental Knee Arthroplasty*,
https://doi.org/10.1007/978-3-030-27411-5_13

The Mechanism of Sensing Pain

Our understanding of the pathway of pain transmission has improved over the past 20 years. As a result, our ability to develop and utilize targeted agents for the treatment of acute pain has been enhanced. Pain signal transmission begins in the periphery at the time of surgical incision. Direct damage to tissue results in the liberation of multiple substances including phospholipids from damaged cell walls. They are converted to arachidonic acid by phospholipase A_2, which in turn, is converted to a number of pro-inflammatory mediators, the most clinically significant being prostaglandins (PGs), which are produced by cyclooxygenase-2 (COX-2). Cells lack the ability to store PGs, which results in their immediate release, sensitizing peripheral nociceptors to mechanical and chemical stimuli. In addition, ion channels on these nerves are activated by ATP, which is released from epithelial cells. The combination of ion channel activation and nociceptor sensitization alters the resting membrane potential and influences the likelihood of depolarization and signal transmission along these neurons, primarily Aδ and C fibers. The process of *peripheral sensitization* occurs at this location when nociceptors that have a high threshold for depolarization are activated by the combination of these neurochemical events.

These fibers transmit signals to the spinal column where they enter the spine at a location determined by the dermatome, myotome, or sclerotome responsible that has received the nociceptive signal from the periphery. They synapse with second-order neurons that cross to the contralateral side of the spinal cord and ascend via the spinothalamic tract (STT). At this synapse, an interneuron modulates the ascending signal. Interneurons are part of a network of descending tracts that excrete both excitatory and inhibitory substances at the junction of the primary and secondary afferent neurons in the dorsal horn of the spinal cord. Additionally, this is a site where COX-2 is expressed, again producing the pro-inflammatory PGs, resulting in increased release of neurotransmitters from the primary afferent neurons, interference with glycine receptor (impairing the inhibitory actions of the neurotransmitter), and directly depolarizing the secondary afferent neurons in the STT. It is in the dorsal horn of the spinal cord where repetitive noxious stimulation results in a cumulative increase in signaling, with the end result being hyperalgesia. This process is known as *wind up*. The N-methyl-D-aspartate (NMDA) receptor also has a role at this level. When blocked, the summation of response is blunted and returns to normal.

Neurons of the STT project to higher structures after first synapsing in the thalamus. From there, neurons travel to the sensory cortex, the limbic system, and other subcortical areas. The limbic system connections mediate the autonomic and arousal responses seen with pain stimuli. *Central sensitization* is a state of hyperexcitability within the nociceptive reflexes pathway. Long-term exposure to nociceptive input can result in remodeling of the somatosensory cortex, with expansion of cutaneous receptive fields. Descending pathways from the brainstem are normally in a tonic state of inhibition. The neurotransmitters norepinephrine and serotonin are the main mediators of this signal. The descending pathway applies a signal on the interneurons located in the dorsal horn of the spinal cord. When there is release from this state of inhibition, there is, in turn, a state of excitability that leads to further ascending nociceptive signaling. The ability of this complex, interconnected signaling pathway to dramatically increase nociceptive activity should not be underestimated. This is clinically reflected by the variability between individual patient's pain perceptions even if undergoing the same surgical procedure.

Identifying Preoperative Risk Factors

Along with a greater understanding of the pathway of pain transmission, we are beginning to understand some of the characteristics that increase the risk for poorly controlled postoperative pain. A comprehensive review of these risk factors in the setting of total knee arthroplasty

(TKA) has yielded several significant outcomes: higher levels of catastrophizing, higher levels of preoperative pain, greater number of pain sites, depression and/or anxiety, and poorer levels of preoperative function. The strongest predictors are catastrophizing and presence of pain at sites other than the knee.

Catastrophizing has been described as the tendency to misinterpret and exaggerate situations that may be threatening. With regard to pain, the same aberrant response manifests with an exaggerated negative perception to a painful stimulus. At the time that it was first introduced as a concept, Sullivan and colleagues provided a questionnaire (see Fig. 13.1) that aids the physician in the diagnosis of catastrophizing. Higher scores equate to greater risk for persistent postoperative pain. It has been reported that a score above 30 equates to the 75th percentile in a group of injured workers; of these workers, 70% considered themselves disabled. It should be noted that the questionnaire can be divided into three domains: rumination, magnification, and helplessness. Previous studies regarding chronic pain following TKA have shown the rumination items (8, 9, 10, 11, highlighted in yellow in Fig. 13.1) to be the most predictive of persistent pain at 2 years. Patients with a score of 3.3 ± 2.1 on these items had no pain versus those with a score of 5.6 ± 3.7 experi-

	Not at All	To a Slight Degree	To a Moderate Degree	To a Great Degree	All the Time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4
I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

Fig. 13.1 Pain catastrophizing questionnaire. (From Sullivan et al. [6])

enced chronic postoperative pain. Knowing this is helpful but more important is how to modify this risk factor. In the absence of intervention, catastrophizing remains stable. However, participation in targeted psychological therapy, such as cognitive behavioral therapy, has been shown to reduce scores associated with catastrophic thinking. Depression and anxiety will not be discussed in this section, but it should be noted that many symptoms of these illnesses overlap with items in the catastrophizing questionnaire.

Knee pain is the most common reason patients consider knee joint replacement. Reviewing the risk factors mentioned above, one could extrapolate that increased pain scores and pain at sites other than the knee may be seen as indicators that some degree of sensitization (peripheral and/or central) has occurred. Taking this into account, many patients presenting for evaluation for arthroplasty will be on some form of oral analgesics. While the use of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) prior to surgery appears safe, the use of opioids prior to surgery has been correlated with worse patient-reported outcomes, including pain scores. Long-term use of opioids leads to the development of a phenomenon referred to as *opioid-induced hyperalgesia (OIH)*. OIH is an under-recognized state of nociceptor sensitization that results in a paradoxical response to opioid analgesics – escalating doses of opioids leads to more pain. The exact mechanism of this process is unknown. It is important to recognize and take into consideration that these patients, reporting significantly higher pain scores prior to surgery, are unlikely to achieve satisfactory pain relief following surgery. Determining the proper timing of operating on a patient with multiple risk factors requires careful consideration of the risk–benefit ratio. While surgical correction is the ultimate therapy in these settings, it should be noted that there are additional methods of reducing knee pain prior to arthroplasty to consider. These include physical therapy (PT), viscosupplementation, intra-articular steroids, and genicular nerve radiofrequency denervation.

Clinical Case Questions

- **What are the risk factors for this patient having poorly controlled postoperative pain?**
  - This patient has a high preoperative pain score (9/10), pain at multiple other sites (fibromyalgia), may have maladaptive thought processes (given history of depression), and is on preoperative opioids.
- **What can be done preoperatively to optimize this patient from a pain perspective?**
  - It would be prudent to administer a pain catastrophizing questionnaire. If she does score high, it would be worthwhile to address her fears associated with surgery and pain. It may be necessary to obtain the help of a mental health provider to administer cognitive behavioral therapy or graded exposure therapy. Her fibromyalgia pain symptoms should be under reasonable control and stable prior to proceeding with surgery. Lastly, it is ideal to wean opioids prior to surgery. To help facilitate this, one could perform an intra-articular steroid injection and she should be instructed to follow up with the prescriber of her opioids to have them weaned to the lowest dose possible.

Consequences of Poorly Controlled Postoperative Pain

Identifying and addressing risk factors for poorly controlled acute postoperative pain is essential in optimizing outcomes following UKA. The specter of poor postoperative pain control has many aspects: chronic pain, impaired function, delayed recovery from surgery, reduced quality of life, prolonged opioid use, and increased medical costs. Acute postoperative pain can affect other organ systems including cardiovascular (myocardial infarction), pulmonary (splinting, atelectasis, and pneumonia), gastrointestinal (nausea, vomiting, reduced motility, and ileus), and renal (urinary retention), leading to additional morbidity. Chronic pain also leads to impairments in sleep and mood, worsening preexisting anxiety or depression.

Chronic pain is the presence of pain beyond 3 months following the inciting event. Incidence of chronic pain across the spectrum of surgical procedures varies depending on the surgery in question. Although the incidence of chronic pain following UKA is unknown, the rate of chronic pain following TKA has been estimated as high as 20%. These patients are often unable to participate fully in PT, leading to poor functional outcomes.

Anesthesia for UKA and Techniques for Postoperative Pain Control

Anesthesia for UKA should routinely involve regional anesthesia techniques. This comes in many forms, each of which has pros and cons, which will be discussed in this section.

Neuraxial Blocks

Neuraxial blocks refer to the administration of local anesthetics that occur at sites within the spinal column. The two locations for blocks are the epidural space (between ligamentum flavum and dura mater) and the subarachnoid (also known as spinal) space. Administration of local anesthetics in the epidural space results in a slow-developing anesthetic. The dose required to achieve an adequate level of anesthesia is larger (compared to a subarachnoid block). A subarachnoid block results in rapid onset of an anesthetic, with a more complete motor blockade and faster developing hemodynamic effects compared to an epidural block. Neuraxial blocks can be a single dose (a.k.a. single shot) or continuous (via a temporarily-placed catheter). Adverse effects of neuraxial blocks are uncommon but can include pain at the site of injection, headache, bleeding, infection, and nerve damage. A review of more than 100,000 neuraxial anesthetics for total joint arthroplasty demonstrated no serious injuries from single-shot spinal anesthetics. Epidural hematomas were rare when an epidural catheter was placed, occurring at a rate of 1:7857; in these patients, there were several factors that contributed to the development of a hematoma, including altered coagulation parameters and use of antiplatelet/anticoagulant medications. The American Society of Regional Anesthesia (ASRA) has provided guidelines to minimize the risk of bleeding during neuraxial blocks and was not necessarily followed for these specific cases. Aside from adverse effects, there are many expected side effects from neuraxial blocks, which are related to the site of blockade and the pharmacological agent injected. Injection of local anesthetics results in reduced blood pressure, lower extremity numbness, lower extremity weakness, and urinary retention. All of these effects are limited, and their duration is directly related to the dose and specific local anesthetic administered. For example, spinal bupivacaine, administered in doses of up to 10 mg, generally produces these effects for up to 2–3 hours. Other medications used for neuraxial blocks include opioids and clonidine. Both of these can provide additional analgesia when local anesthetics alone fail to provide adequate pain relief; they augment the effects of local anesthetics but cannot be used alone for surgical anesthesia. The potential for prolonged weakness is something to take into account when choosing the dose of a spinal anesthetic and the setting in which the UKA is being performed (hospital versus ambulatory surgery center) and planned postoperative disposition. Of note, the benefits of neuraxial blocks far outweigh the use of general anesthesia; despite the potential for delayed weakness, patients receiving neuraxial blocks have fewer postoperative falls after knee replacement. The benefits of neuraxial blocks do not end there. Compared to general anesthesia, neuraxial blocks for knee arthroplasty reduce the incidence of 30-day mortality and morbidity such as pneumonia, pulmonary embolism, renal failure, and respiratory failure. There are also lower rates of blood loss, rates of blood transfusions, and surgical site infections.

Peripheral Nerve Blocks

Among the many ways of controlling postoperative pain, there are a variety of peripheral nerve

blocks. Depending on the dose and specific local anesthetic injected, these blocks can provide extended analgesia that allows patients to mobilize early and achieve early discharge following surgery. Targeting the correct nerves is critical, as a preference for sensory nerves is prioritized in order to prevent weakness associated with mixed motor/sensory nerves. The femoral, saphenous, sciatic, obturator, and lateral femoral cutaneous nerve blocks have all been studied for their use in providing analgesia knee arthroplasty. I should caution the reader that the evidence that supports use of these blocks is in *total* knee arthroplasty. However, the techniques described can be generalized to apply to the UKA patient.

Common approaches to UKA include mid-vastus and medial parapatellar. With these approaches, pain is transmitted along the saphenous nerve (infrapatellar branch), medial vastus muscle nerve (terminal branch), and femoral cutaneous nerve (anterior branch). Within the joint itself, distal elements from the obturator and tibial nerves combine to form the popliteal nerve plexus. This plexus innervates the menisci, perimeniscular joint capsule, posterior knee capsule, cruciate ligaments, and infrapatellar fat pad.

In the past 5 years, blockade of the saphenous nerve within the adductor canal of the thigh (AC block) has become an effective modality for both surgeons and anesthesiologists in aiding early ambulation and providing excellent analgesia. Given the ease with which the block can be performed with the low likelihood of motor blockade, the AC block has largely replaced the femoral nerve block in clinical practice. The adductor canal is an anatomical space in the thigh that is bordered by the sartorius muscle (superiorly), vastus medialis muscle (medially), and adductor longus/magnus muscles (medially). Within this musculoaponeurotic canal, the saphenous nerve travels with the superficial femoral artery and vein distally toward the adductor hiatus on the medial aspect of the lower thigh. An ideal location of the block has been postulated, and many authors agree that the medial thigh (approximately halfway between the anterior superior iliac spine and base of the patella) is that location. At this site, one can block the saphenous nerve only. Despite the close proximity of the medial vastus muscle nerve, it travels within a separate aponeurotic sheath and cannot be anesthetized simultaneously with an AC block. Ultrasound guidance facilitates recognition of the critical structure involved with an AC block, making it not only effective but also easily accomplished. A recent meta-analysis concluded that compared with femoral nerve blocks, AC blocks have been proven to preserve quadriceps strength without compromising analgesia. Small volumes are often effective and preferred. The borders of the adductor canal are dense, and higher injection volumes are associated with spread to less desirable sites. Proximal spread will lead to blockade of the femoral nerve, including the motor components, causing quadriceps weakness. Similarly, posterior spread of adductor canal injectate has been described, causing blockade of the sciatic nerve leading to foot drop.

The obturator nerve has historically been associated with variable success, as landmark-based techniques often lead to inaccurate sites of local anesthetic injection. However, with the routine use of ultrasound guidance, one can more reliably identify the intermuscular plane between the pectineus and external obturator muscles along the medial aspect of the inguinal ligament. A small volume of injection is all that is necessary to accomplish the block and avoid spread to adjacent neurological structures. Alone, an obturator nerve block (ONB) would not provide adequate analgesia following UKA. However, a recent randomized, controlled trial comparing the combination of ONB plus AC block to AC block alone resulted in superior pain relief in the combination group. The superior analgesia was offset by adductor weakness, the clinical significance of which is unknown, as the study did not document postoperative falls or time to discharge as endpoints.

The sciatic nerve divisions contain fibers that innervate the posterior aspect of the knee. There have been many studies in TKA patients comparing the addition of a sciatic nerve block (SNB) to femoral nerve block. A meta-analysis investigating the efficacy of such a combination of blocks has shown that the combination of blocks has

the ability to reduce pain early (12 and 24 hours) after surgery. The all-important question of promoting lower extremity weakness by performing SNB for these patients has unfortunately not been answered. In the published studies, there are no quantitative measures of dorsiflexion and plantar flexion strength, incidence of falls, and time to meet discharge criteria.

Given the need to address the posterior innervation of the central elements of the knee, many surgeons have made it routine practice to perform a periarticular injection (PAI) of local anesthetic alone or in combination with epinephrine, non-steroidal anti-inflammatory drugs (NSAIDs) and, in some cases, opioids. PAI is relatively safe, simple, and quick, as it is performed by the surgeon intraoperatively prior to closure. The use of PAI has been shown in some randomized, controlled trials to have similar analgesia to peripheral nerve blocks (femoral plus SNB) without the drawbacks of weakness that would impair early ambulation. These results are encouraging, but work remains to identify the ideal combination of local and regional anesthesia for these patients. There have not been investigations on blocks that avoid weakness (i.e., AC blocks) in combination with PAI that might accomplish superior analgesia and maintain motor strength allowing for early mobilization and expedited discharge. Another important aspect of PAI is what a surgeon injects – local anesthetics have been studied to a small degree and we do know that ropivacaine and bupivacaine have equianalgesic effects compared to liposomal bupivacaine.

Although rare, complications associated with nerve blocks include the possibility of nerve damage, bleeding, local anesthetic systemic toxicity (LAST), local anesthetic myotoxicity, and infection. The rate of long-term nerve damage following a peripheral nerve block has been estimated at 2–4 per 10,000 blocks. Unfortunately, the widespread adoption of ultrasound guidance has not altered this number, as incidence has remained stable over the past two decades. Bleeding at the site of injection remains rare; utilizing the ASRA guidelines for regional anesthesia has aided in minimizing this morbidity. LAST occurs when the injected local anesthetic solution reaches circulation via intravascular uptake or direct injection. This can result in seizures, arrhythmias, and cardiovascular collapse. In patients undergoing TKA, a meta-analysis concluded that LAST occurs at a rate of 0.68% with an overall decreasing trend. Treatment has been well described and involves administration of lipid emulsion. Local anesthetic myotoxicity is a complication of peripheral nerve blocks that has long been known, but for the sake of patients undergoing knee surgery, it was previously inconsequential. Myotoxicity manifests as necrosis of skeletal muscle with associated profound weakness. Although previously described with retrobulbar blocks, the problem seems to have resurfaced with the widespread adoption of the AC block. There are now multiple case reports of local anesthetic-induced myotoxicity following AC blocks in patients undergoing knee surgery. It is not completely understood why this block is associated with myotoxicity, but one should note the local anesthetic chosen for the block does have importance. In order of increasing toxicity, lidocaine, ropivacaine, and bupivacaine (including liposomal or microsphere formulations) have all been associated with myotoxicity. Higher concentrations and longer duration of exposure (i.e., continuous infusion) also correlate with this phenomenon. Recovery is possible but can take up to one year and aggressive physical therapy to achieve.

Clinical Case Question

- **What would be an appropriate anesthetic plan?**
  - This patient is an appropriate candidate for neuraxial anesthesia in the form of a single-shot spinal block with 10 mg isobaric bupivacaine. She is not on anticoagulants, and her prior spine surgery does not preclude this anesthetic approach. Prior to the spinal anesthetic, she should be given a single-shot AC block with 20 mL 0.5% ropivacaine with epinephrine 1:200,000 to provide for extended analgesia after her spinal anesthetic wears off (Table 13.1).

Table 13.1 Example of anesthetic plan for unicompartmental knee arthroplasty

	Preoperative (holding area)	Intraoperative (OR)	Postoperative (recovery room)
Medications	Pregabalin 100 mg PO Acetaminophen 1000 mg PO Celecoxib 400 mg PO	Dexamethasone 0.1 mg/kg IV (up to 10 mg) Ketamine 0.5 mg/kg IV (via bolus or divided doses) Ketorolac 15 mg IV Ondansetron 4 mg IV IV fluids titrated per hemodynamics Propofol infusion titrated for patient comfort	Oxycodone 5 mg every 4–6 hrs PRN
Regional anesthesia	Single-shot adductor canal block (20 mL 0.5% ropivacaine with epinephrine 1:200,000) Single-shot spinal anesthetic (10 mg isobaric 0.5% bupivacaine)		

Perioperative Medications Management of Acute Pain Following UKA

Medical management of acute pain is best accomplished by employing multimodal analgesia (MMA). MMA has been proven to provide superior analgesia and patient satisfaction compared to single-agent strategies. MMA is the method of combining analgesic medications with differing mechanisms of action with the intention of obtaining an additive or synergistic effect. While opioids are not excluded from this strategy, the addition of nonopioid medications (adjuvants) permits the use of lower dose necessary of opioids. These adjuvant medications enhance analgesia and minimize potential adverse effects.

Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Although the exact mechanism by which acetaminophen produces its analgesic effect is unknown, it has been postulated that it inhibits central prostaglandin synthesis. Despite a likely similar mechanism of action, acetaminophen differs from traditional NSAIDs in that it has a relatively weak anti-inflammatory effect in the periphery, inhibits COX poorly at surgical sites, and has no effect on platelet function or the gastric mucosa. Systematic reviews have demonstrated that acetaminophen has similar effects in reducing postoperative pain after orthopedic procedures compared to traditional NSAIDs. But more importantly, the combination has demonstrated a synergistic effect.

Acetaminophen has gained popularity in the perioperative setting, as an intravenous (IV) formulation has become available. The major difference between IV and oral acetaminophen is that IV acetaminophen has a faster time to peak effect and higher peak serum and CSF concentrations. However, a superior clinical outcome with the use of the IV formulation has not been demonstrated at this time. The dramatic difference in cost may favor the use of the oral formulation. Oral acetaminophen has been used successfully in outpatients for acute pain. Of note, it is quite common for acetaminophen to be used in combination with short-acting opioids (e.g., hydrocodone/acetaminophen, oxycodone/acetaminophen), headache medications (e.g., aspirin/caffeine/acetaminophen), and common cold medications (dextromethorphan/phenylephrine/acetaminophen). There have been recommendations of a maximum daily dose to 3000 mg per day. A proposed dosing scheduled of 1000 mg every 8 hours appears safe as long as patients are not consuming acetaminophen from another source. The choice of 1000 mg does have signifi-

cance; compared to 650 mg, the 1000 mg dose confers superior analgesia.

Contraindications for acetaminophen include active liver disease or known allergy. Like NSAIDs, there is no need to taper or wean acetaminophen; it can be stopped abruptly without concerns of withdrawal.

NSAIDs are a very common analgesic medication and have a significant role in the perioperative setting. Surgical damage of tissue leads to the production of prostaglandins by the cyclooxygenase-2 (COX-2) enzyme. As mentioned previously, prostaglandins are important chemicals that initiate peripheral sensitization. NSAIDs acetylate the COX-2 enzyme and reduce prostaglandin formation and attenuate the hyperalgesic response.

Use of COX-2 inhibitors in the perioperative period has consistently demonstrated reduced postoperative opioid consumption, lower pain scores, and improved range of motion following total joint replacement. It is ideal to continue a COX-2 inhibitor after major surgery for a period of at least 2 weeks, as this timeframe coincides with the duration of the post-surgical inflammatory process. It is ideal to administer NSAIDs prior to surgery in order to obtain an effective blood level of the drug. A common practice is administering celecoxib 400 mg preoperatively on the day of surgery, followed by 200 mg every 12 hours postoperatively for a duration of 2 weeks. Alternatively, one could use one of many other NSAIDs. But it should be noted that the inhibition of COX-2 differs between individual NSAIDs. Meloxicam and celecoxib are on one end of the spectrum with the most COX-2 selectivity, while ketorolac and aspirin are the opposite (with a strong preference for COX-1).

It would be reasonable to continue both acetaminophen and NSAIDs until physical therapy has been completed. Like acetaminophen, celecoxib and other NSAIDs do not need to be weaned or tapered; they may be stopped without concern of precipitating withdrawal.

NSAIDs have demonstrated no increase in major bleeding events following TKA. Therefore, it is considered to be safe for patients on anticoagulation for deep venous thrombosis prophylaxis to continue NSAIDs. Contraindications to specific NSAIDs include allergy to aspirin and other NSAIDs as well as to sulfonamides. Avoid NSAIDs in patients with renal insufficiency or renal failure, and in patients older than 70 years, the dose should be reduced by half.

Neuropathic Medications (Anticonvulsants)

The anticonvulsant class of medications includes both gabapentin and pregabalin. These medications have been shown to be effective in treating acute postoperative pain. Both medications exert their effects by binding to and modulating $\alpha_2\delta$ voltage-dependent calcium channels. The end result is thought to be an inhibition of calcium influx via these channels, subsequently inhibiting the release of excitatory neurotransmitters. Additionally, these receptors may play an important role in the development of chronic pain; presynaptic voltage-gated calcium channels are upregulated in the dorsal root ganglion (DRG) playing a role in *wind up* following surgery; as mentioned previously, this is one of the processes by which chronic pain develops. In fact, animal models demonstrate the ability of pregabalin to reduce postoperative hyperalgesia.

The major advantages of pregabalin over gabapentin are greater bioavailability, increased lipid solubility (improving diffusion across the blood–brain barrier), and fewer drug interactions (due to absence of hepatic metabolism). The combined result is a more potent medication; pregabalin achieves efficacy at lower doses. The difference in bioavailability cannot be stressed enough. Gabapentin requires active transport across the gastrointestinal mucosa; doses of gabapentin 300 mg three times per day have approximately 60% oral bioavailability, whereas pregabalin has ≥90% oral bioavailability. Increasing doses of gabapentin do not necessarily translate to improved bioavailability; 1200 mg, 2400 mg, and 3600 mg dosages (divided three times per day) have 47%, 34%, and 33% bioavailability, respectively. It should come as no surprise that esca-

lating doses of gabapentin does not necessarily result in improved analgesia.

Perioperative use of pregabalin can decrease the incidence of chronic pain after TKA. Preoperatively, patients should be given a single dose of 100–150 mg pregabalin followed by 50–75 mg every 8–12 hours for 2 weeks postoperatively to achieve this. Studies of perioperative gabapentin use have been more heterogeneous, and there has been a lack of uniformity in dosing. Lack of clinical efficacy in the perioperative period is in all likelihood due to the aforementioned limitations of variable bioavailability and blood levels of the drug. Anticonvulsants may be continued, if the patient experiences continued pain following UKA. Contraindications for anticonvulsants include allergy to the compound itself or other medications in the same class. Doses should be reduced in patients with reduced renal function and in the elderly. Caution is advised when prescribing anticonvulsants to patients with mental illness, as these drugs have the potential to alter mood, worsening symptoms of depression.

Both gabapentin and pregabalin should be weaned, as abrupt cessation can lead to central nervous system hyperexcitability, causing irritability, restlessness, anxiety, and seizures. For example, a patient taking pregabalin 50 mg three times per day would reduce their dose to 50 mg twice per day, then to 50 mg once daily prior to stopping the drug altogether. That said, with such low doses of these drugs given for limited amounts of time, symptoms of withdrawal are unlikely to manifest.

Glucocorticoids

Administration of steroids in the perioperative period can modulate peripheral inflammatory pathways. As a component of MMA, steroids have been shown to reduce acute pain. Timing of administration appears to be most effective if steroids are administered prior to the surgical stimulus. While optimal doses have been debated, some have obtained a beneficial effect by administering dexamethasone 16 mg IV; one half of the dose has had mixed results. A recent meta-analysis has addressed this question and confirmed that a single dose of 10 mg dexamethasone IV prior to surgical incision will result in a reduction in acute pain for up to 48 hours without any adverse effects in patients undergoing TKA. The safety profile of a single dose of corticosteroids has been established by prior reviews and should reassure providers hesitant to administer steroids to a surgical patient. Caution is advised in diabetic patients, as steroids will certainly cause elevations in blood glucose.

Ketamine

Ketamine is a noncompetitive NMDA receptor antagonist. As mentioned previously, the NMDA receptor has an important role in the transmission of pain and the *wind up* process. As part of a multimodal regimen, ketamine has been shown to decrease opioid consumption and lower pain scores following surgery. This finding is part of a growing body of evidence that low-dose ketamine may play an important role when used as an adjunct to opioids, local anesthetics, and other analgesic agents.

One of the more impressive abilities of ketamine is its ability to reduce the incidence of chronic pain in patients undergoing a variety of procedures; a single dose of ketamine 0–0.5 mg/kg followed by an intraoperative and postoperative infusion of 0.7–4.2 mcg/kg/min was able to demonstrate fewer cases of persistent postsurgical pain at 6 months postoperatively in these cases. A meta-analysis of these data supported not only a pre-incisional bolus and intraoperative infusion but also an infusion for up to 24 hours. In a study of opioid-experienced patients undergoing spine surgery, ketamine at a dose of 0.5 mg/kg bolus followed by an intraoperative ketamine infusion of 10 mcg/kg/min resulted in reduced pain scores at 6 weeks. This is truly an impressive result, as the opioid-experienced patient often presents a challenge to both surgeons and anesthesiologists.

Side effects of ketamine are expected at doses ≥2 mg/kg, leading to psychomimetic effects that include hallucinations, nightmares, cogni-

tive dysfunction, or excessive sedation. Low-dose ketamine (<1 mg/kg total dose) appears to be associated with less adverse effects and may allow physicians to harness the benefits of perioperative ketamine without provoking its unwanted adverse effects.

Opioids

Opioid receptors are found at multiple sites within the central nervous system. Activation of the opioid receptors results in the reduction of excitatory neurotransmitter release from the presynaptic membrane secondary to the inhibition of voltage-gated calcium channels. Although use of opioids has been commonplace for postoperative pain management, the development of fast track and enhanced recovery protocols seeks to minimize their use.

Opioids come in two formulations, long-acting and short-acting versions. This is important to note as pharmacodynamics vary between the two and have the potential for causing respiratory depression and death. Short-acting opioids are the most commonly prescribed type of opioid for pain following UKA. Examples include tramadol and the combinations hydrocodone/acetaminophen and oxycodone/acetaminophen. One of the drawbacks to using combination products is the addition of acetaminophen to the opioid, which impacts the total daily dose of acetaminophen consumed. Only oxycodone comes in an immediate-release version without acetaminophen. Patients can be prescribed oxycodone immediate-release 5 mg or 10 mg every 4–6 hours on an as-needed basis for breakthrough pain. Patients should be encouraged to take this medication 1 hour prior to physical therapy. One hour seems an ample amount of time to allow patients to reach an effective blood level of the drug at the time of therapy. Short courses of opioids should be prescribed, and physicians should consult their state's prescription monitoring database to assure the patient has not received additional controlled substances that would put them at risk of over-sedation, respiratory depression, and death. Additionally, a prescriber should detail the patient's past experience with opioids including history of abuse or addiction. The potential for a recovering addict to relapse with a short course of postoperative opioids is real and can have devastating consequences. If concerned, a surgeon should consult a pain physician and possibly a psychiatrist preoperatively for assistance in managing the patient's acute postoperative pain and addiction.

Weaning opioids should be done in a systematic manner to avoid possible withdrawal. Short-acting opioids are prescribed to be taken on an intermittent, or "as-needed," basis. This requires the patient to consume the medication only when they have pain or prior to an activity that is anticipated to produce significant pain (i.e., physical therapy). After 2 weeks, weaning can begin on an individual basis. During the acute and subacute phases of postsurgical pain, patients should be weaned to the lowest effective dose of short-acting opioids. This means that patients are taking the lowest cumulative dose of opioids per day as is necessary to participate in physical therapy and to perform the same activities of daily living they were prior to surgery.

Withdrawal from opioids is an uncomfortable experience that occurs with abrupt cessation of opioids in patients consuming high doses or in cases of prolonged use. Early opioid withdrawal symptoms include agitation, anxiety, myalgias, insomnia, rhinorrhea, or diaphoresis. The symptoms of withdrawal can continue for weeks, although this is uncommon with opioid use for acute postoperative pain. Late symptoms include nausea, vomiting, abdominal pain, diarrhea, mydriasis, hypertension, tachycardia, and formication. Oral and transdermal clonidine have been used to combat the early effects of withdrawal, as it provides anxiolysis and blunts the increase in sympathetic activity; antidiarrheal and antinausea agents are often prescribed for patient comfort.

Metabolism of opioids is carried out in the liver. Opioids are converted to water-soluble metabolites, many of which remain biologically active, which are excreted by the kidneys. Any degree of renal insufficiency results in the accumulation of these metabolites and their unwanted effects such as myoclonus, respiratory depres-

sion, and seizures. Caution should also be exercised in patients with a history of obesity and obstructive sleep apnea (OSA).

The opioid epidemic has garnered much deserved attention. The scrutiny over prescribing of postoperative opioids should not come as a surprise. The Centers for Disease Control and Prevention recommend doses of no more than 50 mg morphine equivalent dose for acute postoperative pain. This statement should be taken with a grain of salt; the statement does not offer suggestions based on the surgical procedure performed or based on individual characteristics. It is prudent for the prescriber to take this into account, along with the known risk factors associated with adverse effects (including death) from opioids. These include concurrent use of benzodiazepines, marijuana, tobacco, alcohol, presence of psychiatric disorder (depression/anxiety), coronary artery disease, arrhythmia, history of substance abuse or aberrant medication taking behaviors, or impulse control problems (Table 13.2).

Table 13.2 Example of postoperative oral pain regimen following unicompartmental knee arthroplasty

Drug	AM	PM	QHS	AM	PM	QHS
	Day of surgery			**POD 1–8**		
Oxycodone IR 5–10 mg	PRN every 4–6 hours			PRN every 4–6 hours		
Acetaminophen 1000 mg		X	X	X	X	X
Celecoxib 200 mg	XX* (2 tabs)			X	X	
Pregabalin 50 mg	XX* (3 tabs)			X	X	X
	POD 9			**POD 10–13**		
Oxycodone IR 5–10 mg	PRN every 6 hours			PRN every 6 hours		
Acetaminophen 1000 mg	X	X	X	X	X	X
Celecoxib 200 mg	X	X		X	X	
Pregabalin 50 mg	X	X	X	X	X	X
	POD 14			**2–6 weeks postoperative**		
Oxycodone IR 5 mg	PRN every 8 hours			PRN QD with PT		
Acetaminophen 1000 mg	X	X	X	TID PRN		
Celecoxib 200 mg	X			Daily PRN		
Pregabalin 50 mg	X	X	X (stop on POD 15)			

*should be given preoperatively

Clinical Case Question

- **How does one successfully manage opioids prescribed after surgery?**
  - A prescription for opioids should begin with an agreement between patient and prescriber. At minimum, a verbal discussion of the risks and benefits of the drugs should take place; some practices utilize a formal document that is signed by both physician and patient. This document describes how the physician intends the medication to be used with warnings about the misuse and abuse of the drugs. It also sets expectations for the patient, knowing that opioids will not be continued if they fail to provide a meaningful benefit. A urine drug screen can be taken, with the intention to screen for unreported substances that could increase the risk for respiratory depression. Prior to writing a prescription for opioids, a physician should inspect their local controlled substance monitoring database. The database will offer insight as to what controlled substances the patient is receiving, from whom, and what dose/quantity. This will allow the surgeon to make an informed decision when providing any postoperative opioids. As stated above, the lowest effective dose of opioids should be utilized. This will likely vary from patient to patient; regular re-evaluations are necessary to ensure efficacy and allow for discussions of reducing postoperative opioids and potential barriers to weaning.

Postoperative Considerations

A successful UKA is one that ends with the restoration of function and reduction of pain. For many patients, this is in fact the case. For the unfortu-

nate few, with ongoing pain and failure to achieve adequate range of motion, further intervention is often needed. Aggressive and early intervention, in the form of medical management and physical therapy, can be helpful. The same can be said for knee manipulation. Without satisfactory management of pain symptoms, a full recovery may not be possible. Involvement of a pain specialist gives the opportunity for evaluation of a sympathetically-mediated processes, optimization of a medical regimen, and discussion for interventional therapies that may improve the outcome.

Unicompartmental knee osteoarthritis is a common problem with a proven and reliable treatment in the form of UKA. An understanding of the anatomical basis of pain and the pharmacologic agents used as part of MMA protocols to interrupt these pain pathways will assist the surgeon in creating a successful, expedited recovery for their patients. Anesthesia for UKA can be equally important in reducing morbidity and allowing for rapid recovery. Communication with the anesthesiology team is essential; a strong working relationship between anesthesiologist and surgeon can go a long way in producing a happy, functional patient following UKA.

Clinical Case Question

- **If this patient develops chronic pain, what is the next course of action?**
  - The presence of pain beyond 3 months following surgery is known as chronic pain. These patients require evaluation with a pain physician. Early referral is recommended.

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