25 Nonopioid Pain Medications

LUCY LIN CHEN and JIANREN MAO

KEY POINTS

- With a better understanding of pain pathways and mechanisms, it has been recognized that ion channels play an important role in the transduction, transmission, and modulation of nociceptive signals. This opens a new avenue of developing novel therapeutic agents for the treatment of acute or chronic pain, particularly neuropathic pain.
- Although the exact mechanism of action remains unclear for many drugs listed in this chapter, they often are a component of a multidrug treatment strategy that has been increasingly used for the management of chronic pain conditions.

Introduction

Recent advances in our understanding of pain mechanisms have enabled us to treat acute and chronic pain conditions with a variety of nonopioid pain medications. The option of using nonopioid pain medications is particularly meaningful given the growing global concern over prescription opioid abuse and overdose. Besides acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs), several new categories of nonopioid pain medications can be used for the management of acute or chronic pain and, in particular, neuropathic pain. Examples of these nonopioid pain medications include drugs that block voltage-sensitive sodium channels and voltage-sensitive calcium channels, facilitate opening of chloride channels, increase function of the endogenous γ-aminobutyric acid (GABA) system, and modulate the N-methyl-D-aspartate (NMDA) receptor activity. In particular, ion channel blockers possess the antihyperalgesic effect by targeting specific mechanisms of pathologic pain, although most analgesics in this category do not necessarily produce the typical analgesic effect (i.e., raising the pain threshold above the normal baseline).[1]

This chapter briefly discusses NSAIDs and acetaminophen and focuses on describing several ion channel blockers that are commonly used in the treatment of pain conditions, as listed in Box 25.1. They are grouped into two categories: calcium channel blockers and sodium channel blockers.

Nonsteroidal antiinflammatory drugs

NSAIDs include ibuprofen, naproxen, indomethacin, ketorolac, and diclofenac and are examples of a class of medication commonly used as analgesic to reduce myofascial pain, postoperative pain, and chronic pain conditions. In a recent Cochrane review of 16 randomized, controlled clinical trials (2144 patients), pain relief and function restoration were compared in patients with acute soft tissue injury treated with oral NSAIDs and other oral analgesics including acetaminophen with or without opioids. The analgesic effect was similar between NSAIDs and acetaminophen or opioid, and there were no differences in functional restoration at 7 days,[2] but the patients who were taking opioids reported more adverse side effects.[3] Although acetaminophen, indomethacin, or diclofenac produced similar pain reduction, the combination of acetaminophen and diclofenac showed slightly better pain reduction.[4] Intravenous ketorolac (15 or 30 mg) is a common medication of choice during the early postoperative period if there are no contraindications, such as renal insufficiency.[5] Ketorolac has also been successfully used in pediatric surgical patients.[6,7] A recent metaanalysis also found that NSAIDs were equivalent to opioids or paracetamol in the relief of acute renal colic pain.[8]

The cyclooxygenase-2 (COX-2) inhibitors are considered an alternative to NSAIDs (mixed COX-1/COX-2 inhibitors) while possessing reduced gastrointestinal side effects. However, COX-2 inhibition is associated with increased risk of adverse cardiovascular events, although recent clinical studies, including the data from the PRECISION trial that examined long-term cardiovascular safety issues, support the notion that both NSAIDs and COX-2 carry a certain degree of cardiovascular risk.[9]

Acetaminophen

For many decades, oral acetaminophen has been widely used as an analgesic to treat mild to moderate pain. Recently, intravenous acetaminophen has become available in the United States. Results of a randomized trial of patients who had colorectal surgery indicated that

BOX 25.1 Ion Channel Blockers as Pain Medications (Recommended Dosing)

Calcium Channel Blockers

Gabapentin: Starting dose 100–300 mg/day; titrating up to 1800–3600 mg/day
Pregabalin: Starting dose: 75–150 mg/day; titrating up to 450–600 mg/day
Zonisamide: Starting dose: 50–100 mg/day; titrating up to 450 mg/day
Ziconotide: Starting dose: 0.1 μg/h; titrating up to 0.4 μg/h
Levetiracetam: Starting dose: 250–500 mg/day; titrating up to 2000 mg/day

Sodium Channel Blockers

Lidocaine: Used in a lidocaine test: 1 mg/kg via slow intravenous push or drip
Mexiletine: Starting dose: 150–300 mg/day; titrating up to 600 mg/day
Carbamazepine: Starting dose: 100 mg/day; titrating up to 600 mg/day
Oxcarbazepine: Starting dose: 150 mg/day; titrating up to 900 mg/day
Lamotrigine: Starting dose: 25–50 mg/day; titrating up to 250–500 mg/day
Topiramate: Starting dose: 50–100 mg/day; titrating up to 300–400 mg/day.

intravenous acetaminophen decreased postoperative opioid consumption, reduced hospital stay, improved pain control, shortened time to return of bowel function, and lowered the rate of postoperative ileus.[10] Similar results were found after procedures for posterior spinal fusion,[11] craniotomy,[12] vitrectomy,[13] esophagectomy,[14,15] and total joint arthroplasty.[16]

Compared with an opioids-only option for postoperative pain management in adolescents with idiopathic scoliosis, patients treated with intravenous acetaminophen plus ketorolac consumed less opioids and had less severe constipation.[17] A retrospective analysis of the results of the Premier Database of 61,017 cholecystectomy patients showed that 31,133 (51%) of the patients who received intravenous acetaminophen had experienced a shorter length of hospital stay, a decrease in hospitalization costs, a reduced average daily morphine-equivalent dose, and lower rates of respiratory depression, nausea, and vomiting.[18] However, several studies have failed to show that intravenous acetaminophen achieved the positive results as described here.[19-21] The hepatic side effect is a significant concern for those with long-term acetaminophen use, particularly with alcohol. A recent analysis of nine prospective cohort studies has also linked long-term acetaminophen use with an increased risk of adverse neurodevelopmental outcomes following prenatal acetaminophen exposure.[22]

Calcium Channel Blockers

Opening of calcium channels is an important step of synaptic transmission because it facilitates release of neurotransmitters and neuromodulators from presynaptic sites. Changes in intracellular calcium concentration also modulate cell membrane excitability and initiate a cascade of intracellular responses. Therefore blocking calcium channels can play a significant role in modulating both nociceptive and antinociceptive processes. Drugs that reduce calcium influx into the intracellular compartment of neuronal or glial cells may be used as adjunctive or alternative medications for the treatment of various pain conditions, particularly chronic neuropathic pain conditions. Most calcium channel blockers used as antihypertensive drugs may be suitable for chronic pain management because of their side effects and site of action. Gabapentin, pregabalin, zonisamide, ziconotide, and levetiracetam are examples of drugs that block calcium channels as a part of their mechanisms of action and have been used in pain management.

GABAPENTIN

Gabapentin was initially approved by the U.S. Food and Drug Administration (FDA) as an anticonvulsant (partial seizure) and is currently extensively used for the treatment of neuropathic pain conditions. Although gabapentin's mechanism of action is unclear, it does block voltage-gated calcium channels by binding to the α_2-δ subunit,[23] thereby reducing calcium influx. By blocking calcium influx, gabapentin reduces the release of glutamate and substance P from primary nociceptive afferents, thereby modulating nociceptive transmission. Gabapentin has been used to treat painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, complex regional pain syndrome, and painful peripheral neuropathies caused by human immunodeficiency virus (HIV), cancer, multiple sclerosis, and spinal cord injury.

Painful diabetic neuropathy is a debilitating condition commonly seen in patients with diabetes mellitus. Up to 25% of patients with diabetes may suffer from spontaneous pain, allodynia, hyperalgesia, paresthesias, and other pain symptoms.[24] Postherpetic neuralgia is another common neuropathic pain condition. The incidence of postherpetic neuralgia is estimated to be 9% to 34%, which increases significantly with age. Multiple classes of drugs have been tried to treat pain associated with painful diabetic neuralgia and postherpetic neuralgia, including tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, imipramine, and desipramine. Because of the significant side effects of TCAs, gabapentin has been increasingly used in the treatment of these pain conditions.

Gabapentin is effective in reducing several salient symptoms of neuropathic pain such as burning and shooting pain, allodynia, and hyperalgesia.[25,26] The number needed to achieve at least 50% pain relief with antidepressants and gabapentin are 3.4 and 2.7, respectively.[27] Although both antidepressants and gabapentin may provide moderate pain relief, antidepressants may have more major side effects.

The recommended gabapentin dose range is 1800 to 3600 mg/day, starting at 100 to 300 mg/day and increasing 100 to 300 mg every 1 to 3 days. Adverse effects are usually mild to moderate and typically subside within 7 to 10 days after the treatment is started; however, serious side effects can occur including mood swing, edema, and suicidality. In general, a slow titration process can significantly reduce some otherwise intolerable side effects, such

as dizziness. In addition to its use as a monotherapy, gabapentin has been extensively used in multimodal drug therapy in conjunction with TCAs and other anticonvulsants.[1] Multimodal drug therapy provides better pain control, requiring a smaller dose range for each drug included in the regimen. Gabapentin also can treat complex regional pain syndrome, phantom pain, trigeminal neuralgia, cancer-related neuropathic pain, multiple sclerosis, spinal cord injury, HIV-associated painful sensory neuropathy, and glossopharyngeal neuralgia.

The role of gabapentin in acute postoperative pain management remains unclear.

PREGABALIN

Pregabalin is an anticonvulsant that has a high affinity to the α_2-δ subunit of voltage-sensitive calcium channels. The mechanism of action of pregabalin is similar to that of gabapentin. Pregabalin decreases calcium influx, thereby reducing the release of excitatory neurotransmitters, including glutamate, substance P, and calcitonin gene–related peptide. Pregabalin has no activity on GABA or benzodiazepine receptors; therefore it has no significant drug-drug interactions with such agents.

Pregabalin has been used to treat painful diabetic neuropathy and postherpetic neuralgia, with a significant therapeutic effect.[28,29] It has a quick onset, and, in some cases, pain reduction can be expected on the first day of treatment with pregabalin (300 mg/day). Sustainable sleep improvement is also observed 1 week after the therapy is initiated. Common side effects are dizziness, somnolence, and mild to moderate peripheral edema.[30] Other concerns over pregabalin include behavioral changes such as mood swing and suicidality. Before starting pregabalin, it is recommended to check the baseline creatinine level. Moreover, pregabalin (at an average dose of 450 mg/day) is effective in patients with fibromyalgia, who often have clinical presentations including diffuse musculoskeletal pain, sleep disturbance, and fatigue.

ZONISAMIDE

Zonisamide blocks both voltage-sensitive sodium channels and N-type calcium channels. Studies suggest that zonisamide may be used to treat mania, Parkinson disease, and poststroke central pain or to provide migraine prophylaxis.[31,32] Its possible mechanisms of action include modulation of monoamine neurotransmitter release and free radical scavenging. Zonisamide is effective for the treatment of painful diabetic neuropathy (540 mg/day). The tolerability of zonisamide is difficult to assess because it is often used in multimodal drug therapy. Thus the data on the effectiveness and side effects of zonisamide remain limited.

ZICONOTIDE

Ziconotide is a synthetic peptide analogue of omega conotoxin derived from a marine snail, *Conus magus*. Ziconotide potently and selectively blocks N-type voltage-sensitive calcium channels. This drug is approved only for intrathecal use in patients with severe pain who are refractory to other treatment options, including intrathecal morphine. In early clinical trials, ziconotide exhibited severe central nervous system and psychiatric adverse effects with an initial intrathecal infusion rate of 0.4 μg/h and frequent dosing titration.[33] More recently, ziconotide has been shown to be effective for chronic pain conditions resulting from cancer, acquired immunodeficiency syndrome, and trigeminal neuralgia.[34,35] The role of ziconotide in postoperative pain management is less clear. Given ziconotide's significant side effects and restrictive delivery route, its routine use in acute postoperative pain management is not well justified.

The initial infusion rate of ziconotide should start at 0.1 μg/h intrathecally, with a slow titration of no more than 2 to 3 times the initial dose per week. An implanted intrathecal infusion system is required for the long-term use of this therapy if the initial ziconotide trial is effective.[36] Patients with severe psychiatric disorders may not be proper candidates for this therapy. On the other hand, ziconotide may be advantageous over intrathecal morphine because patients do not develop tolerance after a prolonged use of ziconotide. However, adverse neurologic effects associated with ziconotide therapy will require careful patient selection and monitoring. Using a smaller dose increment may help to avoid systemic toxicity.

LEVETIRACETAM

Levetiracetam is an anticonvulsant approved by the FDA for treatment of epilepsy.[37] Its mechanisms of action are less clear because it may have effects on several neurotransmitter systems, including dopaminergic, glutamatergic, and GABAergic systems. But at least one of its mechanisms of action is due to inhibition of N-type voltage-sensitive calcium channels. Levetiracetam improves neoplastic plexopathies, painful peripheral neuropathy, and postherpetic neuralgia. It also has been used in migraine headache prophylaxis. The dose range is 500 to 2000 mg/day. At this dose range, levetiracetam is well tolerated in clinical trials. Common adverse effects are dry eyes and dizziness.[38]

Sodium Channel Blockers

Sodium channels are primarily involved in nerve conduction. Sodium channels can be divided into two general categories based on their sensitivity to tetrodotoxin (TTX): TTX-sensitive (TTX-S) and TTX-resistant (TTX-R) sodium channels. TTX-S sodium channels are expressed mainly in large and medium dorsal root ganglion neurons, whereas TTX-R sodium channels are expressed mainly in small-diameter dorsal root ganglion neurons, including C-afferent neurons. Expression of both TTX-S and TTX-R sodium channels is likely to be altered when peripheral nerves are injured or severed (axotomy), producing aberrant high-frequency spontaneous ectopic discharges. Sodium channel blockers at a proper dose range are believed to suppress ectopic discharges without blocking normal nerve conduction, which forms the basis of using sodium channel blockers in the treatment of chronic pain conditions, particularly neuropathic pain. Selective Nav 1.7 and Nav 1.8 sodium channel blockers are being investigated for possible clinical applications. Currently, several representative sodium

channel blockers include lidocaine, mexiletine, carbamazepine, oxcarbazepine, lamotrigine, and topiramate.[39]

LIDOCAINE

Lidocaine is a local anesthetic and cardiac antiarrhythmic. Since the 1980s, intravenous administration of lidocaine has been used as a diagnostic tool and, in some cases, a therapeutic tool for intractable neuropathic pain.[39] This treatment modality has been shown to improve chronic pain conditions induced by neurologic diseases, including stroke, neurogenic facial pain, and myofascial pain.[40,41] Up to 78% of cases are associated with a positive outcome when intravenous lidocaine is used.[42] A major pitfall of intravenous lidocaine treatment is its short duration, which requires frequent treatment sessions.

Topical 5% lidocaine patch and over-the-counter topical lidocaine gel or cream provide a local analgesic effect with a minimum systemic effect. Lidocaine patch has been used in patients with neuropathic pain conditions such as painful diabetic neuropathy, postherpetic neuralgia, and peripheral neuropathies. It reduces allodynia and hyperalgesia associated with such conditions.[43] Although the evidence remains weak and unclear, lidocaine patch has been used to treat chronic lower back pain. In some cases, lidocaine patch has become a part of multimodal drug therapy, such as a combination of topical lidocaine patch and gabapentin.[1]

MEXILETINE

Mexiletine is an oral lidocaine congener. It may be used to overcome the shortcoming of transient pain relief with intravenous lidocaine. In many cases, intravenous lidocaine is used as a test to determine whether the intended lidocaine treatment is effective. When a positive response is achieved, oral mexiletine is administered to maintain the therapeutic effect.[44,45] This treatment regimen reduces pain due to painful diabetic neuropathy refractory to other therapies.[46] Mexiletine alone has been used to treat phantom pain and pain after spinal cord injury.[46]

Fibromyalgia and myofascial pain are other clinical conditions that may be responsive to a lidocaine and mexiletine treatment regimen. In addition, anecdotal reports suggest that oral mexiletine may be used to treat primary erythromelalgia, metastasis bone pain, and headaches.

CARBAMAZEPINE

A primary mechanism of action of carbamazepine is sodium channel blockade, which decreases spontaneous firing of Aδ-fibers and C-fibers. Carbamazepine has been approved to treat trigeminal neuralgia, a neuropathic pain condition characterized by episodic lightning, lancinating, or shooting pain along the trigeminal nerve distribution.[47] Carbamazepine has been used for decades and was superior to placebo in a number of clinical trials. It was once considered a "gold standard" and remains a treatment of choice for trigeminal neuralgia, with a response rate of 89% within 5 to 14 days after the treatment is initiated. However, carbamazepine has significant drug-drug interactions and a long list of adverse effects, including central nervous system side effects. In the United States the FDA has issued black box warnings about this drug, including aplastic anemia and agranulocytosis. Therefore its clinical utility is rather limited considering that newer anticonvulsants are available with fewer and less severe side effects.

OXCARBAZEPINE

Oxcarbazepine is an analogue of carbamazepine, which acts as a sodium channel blocker and stabilizes neuronal membrane. In contrast to carbamazepine, oxcarbazepine has fewer drug-drug interactions and side effects, particularly severe blood dyscrasias. The most common side effects of oxcarbazepine are dizziness, drowsiness, hypotension, nausea, and asymptomatic mild hyponatremia. Oxcarbazepine has been used to treat intractable trigeminal neuralgia refractory to other anticonvulsants.[48] With a median dose of 750 mg/day, this novel drug appears to have the same efficacy as carbamazepine in the treatment of trigeminal neuralgia but a much lower incidence of side effects.

Oxcarbazepine also reduces pain associated with painful diabetic neuropathy and complex regional pain syndrome. For patients with postherpetic neuralgia that is unresponsive to carbamazepine and gabapentin, oxcarbazepine, starting at 150 mg/day and titrating up to a maintenance dose of 900 mg/day, may be a promising drug because it significantly reduces allodynia related to postherpetic neuralgia. Oxcarbazepine appears to be well tolerated and may serve as a reasonable alternative to other sodium channel blockers.

LAMOTRIGINE

Lamotrigine has multiple mechanisms of action, although it also blocks both sodium and calcium channels.[49] Lamotrigine is effective in the treatment of trigeminal neuralgia, neuralgia after nerve section, and pain related to HIV neuropathy. With a daily lamotrigine dose of 75 to 300 mg, the intensity of burning and shooting pain is relieved by 33% to 100%, and the frequency of shooting pain attack is reduced by 80% to 100%. In patients with spinal cord injury, lamotrigine decreases overall pain sensation to less than the level of injury in patients with incomplete spinal cord injury but has little effect on spontaneous and evoked pain in patients with complete spinal cord injury.

A typical starting dose for lamotrigine is 25 to 50 mg/day, which can be slowly titrated up over 2 to 3 weeks to 250 to 500 mg/day in divided doses. Tolerability is usually low at high doses (>300 mg/day). Up to 10% of patients may have rashes after taking this medication, with a 3 in 1000 incidence of Stevens-Johnson syndrome. Other side effects are mild dizziness, somnolence, nausea, and constipation.

TOPIRAMATE

Topiramate is another drug that has multiple mechanisms of action. However, at least one of its actions is to block voltage-sensitive sodium channels. It also may potentiate GABA inhibitory action, block voltage-sensitive calcium channels, and inhibit subtypes of glutamate receptors (non-NMDA receptors). Topiramate can cause significant weight loss (up to 7%), a side effect that could be beneficial for

certain patient populations with chronic pain conditions. Topiramate, at a daily dose of 400 mg or greater, attenuates neuropathic pain, improves sleep quality, and reduces body weight.[48] When used to treat chronic lumbar radicular pain, the effect of topiramate is inconclusive because of a high dropout rate and frequent side effects in clinical trials. However, topiramate 30 to 80 mg/day is superior to placebo for the treatment of chronic tension, migraine, and cluster headaches with a substantial tolerability.[50]

Complete references available online at expertconsult.com.

References

1. Vorobeychik Y, et al. *CNS Drugs*. 2011;25:1023.
2. Lyon C, et al. *J Fam Pract*. 2018;67(2):110.
3. Fathi M, et al. *Am J Emerg Med*. 2015;33(9):1205.
4. Woo WW, et al. *Ann Emerg Med*. 2005;46(4):352.
5. Duttchen KM, et al. *J Clin Anesth*. 2017;41:11.
6. Dorman RM, et al. *J Pediatr Surg*. 2017.
7. Marzuillo P. *Acta Paediatr*. 2017.
8. Pathan SA, et al. *Eur Urol*. 2017.
9. Walker C, et al. *Postgrad Med*. 2018;130(1):55–71.
10. Aryaie AH, et al. *Surg Endosc*. 2018.
11. Olbrecht VA, et al. *Clin J Pain*. 2017.
12. Artime CA, et al. *J Neurosurg Anesthesiol*. 2017.
13. Sadrolsadat SH, et al. *Anesth Pain Med*. 2017;7(3):e13639.
14. Ohkura Y, et al. *Medicine (Baltimore)*. 2016;95(44):e5352.
15. Ohkura Y, et al. *Surg Today*. 2017.
16. Sun L, et al. *Medicine (Baltimore)*. 2018;97(6):e9751.
17. Chidambaran V, et al. *Paediatr Anaesth*. 2018.
18. Hansen RN, et al. *Curr Med Res Opin*. 2018:1–7.
19. Sola R, et al. *Eur J Pediatr Surg*. 2018.
20. Towers CV, et al. *Am J Obstet Gynecol*. 2017.
21. Huang PS, et al. *J Arthroplasty*. 2017.
22. Bauer AZ, et al. *Horm Behav*. 2018.
23. Mao J, et al. *Anesth Analg*. 2000;91:680.
24. Backonja MM, et al. *JAMA*. 1831;280:1998.
25. Rauck RL, et al. *J Pain Symptom Manage*. 2013;46:219.
26. Beal B, et al. *Clin Interv Aging*. 2012;7:249.
27. Collins SL, et al. *J Pain Symptom Manage*. 2000;20:449.
28. Lesser H, et al. *Neurology*. 2004;63:2104.
29. Boyle J, et al. *Diabetes Care*. 2012;35:2451.
30. Jensen MP, et al. *Clin J Pain*. 2012;28:683.
31. Bialer M. *Adv Drug Deliv Rev*. 2012;64:887.
32. Kothare SV, et al. *Expert Opin Drug Metab Toxicol*. 2008;4:493.
33. Wermeling DP, et al. *Phamacotherapy*. 2005;25:1084.
34. Backonja MM. *Semin Neurol*. 2012;32:264.
35. Michiels WB, et al. *Clin J Pain*. 2011;27:352.
36. Rauck RL, et al. *Pain Pract*. 2009;9:327.
37. Lukyanetz EA, et al. *Epilepsia*. 2002;43:9.
38. Crepeau AZ, et al. *Expert Rev Neurother*. 2010;10:159.
39. Mao J, et al. *Pain*. 2000;87:7.
40. Nikolajsen L, et al. *Clin J Pain*. 2010;26:788.
41. Carroll I, et al. *Clin J Pain*. 2007;23:702.
42. Peterson P, et al. *Neurol Res*. 1986;8:189.
43. Argoff CE, et al. *Curr Med Res Opin*. 2004;20:S21.
44. Jungehulsing GJ, et al. *Eur J Neurol*. 2013;20:331.
45. Holbech JV, et al. *Eur J Pain*. 2011;15:608.
46. O'Connor AB, et al. *Am J Med*. 2009;122:S22.
47. Cruccu G, et al. *CNS Drugs*. 2013;27:91.
48. Wang QP, et al. *CNS Drugs*. 2011;25:847.
49. Wiffen PJ, et al. *Cochrane Database Syst Rev*. 2011;16(2):CD006044.
50. Hershey LA, et al. *Curr Treat Options Neurol*. 2013;15:56.

References

1. Vorobeychik Y, Gordin V, Mao J, Chen L. Combination therapy for neuropathic pain. *CNS Drugs*. 2011;25:1023–1034.
2. Lyon C, Piggott S, Langner S, DeSanto K. Clinical inquiry: how do oral NSAIDs compare to other oral analgesics right after an acute musculoskeletal injury? *J Fam Pract*. 2018;67(2):110–111. https://doi.org/jfp_6702i [pii].
3. Fathi M, Zare MA, Bahmani HR, Zehtabchi S. Comparison of oral oxycodone and naproxen in soft tissue injury pain control: a double-blind randomized clinical trial. *Am J Emerg Med*. 2015;33(9):1205–1208. https://doi.org/10.1016/j.ajem.2015.05.021.
4. Woo WW, Man SY, Lam PK, Rainer TH. Randomized double-blind trial comparing oral paracetamol and oral nonsteroidal antiinflammatory drugs for treating pain after musculoskeletal injury. *Ann Emerg Med*. 2005;46(4):352–361.
5. Duttchen KM, Lo A, Walker A, et al. Intraoperative ketorolac dose of 15mg versus the standard 30mg on early postoperative pain after spine surgery: a randomized, blinded, non-inferiority trial. *J Clin Anesth*. 2017;41:11–15. https://doi.org/S0952-8180(17)30430-0 [pii].
6. Dorman RM, Ventro G, Cairo SB, Vali K, Rothstein DH. The use of perioperative ketorolac in the surgical treatment of pediatric spontaneous pneumothorax. *J Pediatr Surg*. 2017. https://doi.org/S0022–3468(17)30369-X [pii].
7. Marzuillo P, Calligaris L, Amoroso S, Barbi E. Narrative review shows that the short-term use of ketorolac is safe and effective in the management of moderate-to-severe pain in children. *Acta Paediatr*. 2017. https://doi.org/10.1111/apa.14189.
8. Pathan SA, Mitra B, Cameron PA. A Systematic review and meta-analysis comparing the efficacy of nonsteroidal anti-inflammatory drugs, opioids, and paracetamol in the treatment of acute renal colic. *Eur Urol*. 2017. https://doi.org/S0302-2838(17)30977-6 [pii].
9. Walker C, Biasucci LM. Cardiovascular safety of non-steroidal anti-inflammatory drugs revisited. *Postgrad Med*. 2018;130(1):55–71. https://doi.org/10.1080/00325481.2018.1412799.
10. Aryaie AH, Lalezari S, Sergent WK, et al. Decreased opioid consumption and enhance recovery with the addition of IV acetaminophen in colorectal patients: a prospective, multi-institutional, randomized, double-blinded, placebo-controlled study (DOCIVA study). *Surg Endosc*. 2018. https://doi.org/10.1007/s00464-018-6062-y.
11. Olbrecht VA, Ding L, Spruance K, Hossain M, Sadhasivam S, Chidambaran V. Intravenous acetaminophen reduces length of stay via mediation of postoperative opioid consumption following posterior spinal fusion in a pediatric cohort. *Clin J Pain*. 2017. https://doi.org/10.1097/AJP.0000000000000576.
12. Artime CA, Aijazi H, Zhang H, et al. Scheduled intravenous acetaminophen improves patient satisfaction with postcraniotomy pain management: a prospective, randomized, placebo-controlled, double-blind study. *J Neurosurg Anesthesiol*. 2017. https://doi.org/10.1097/ANA.0000000000000461.
13. Sadrolsadat SH, Yousefshahi F, Ostadalipour A, Mohammadi FZ, Makarem J. Effect of intravenous acetaminophen on postoperative pain in vitrectomy: a randomized, double-blind, clinical trial. *Anesth Pain Med*. 2017;7(3):e13639. https://doi.org/10.5812/aapm.13639.
14. Ohkura Y, Haruta S, Shindoh J, Tanaka T, Ueno M, Udagawa H. Effectiveness of postoperative intravenous acetaminophen (Acelio) after gastrectomy: a propensity score-matched analysis. *Medicine (Baltimore)*. 2016;95(44):e5352. https://doi.org/10.1097/MD.0000000000005352.
15. Ohkura Y, Shindoh J, Ueno M, Iizuka T, Haruta S, Udagawa H. A new postoperative pain management (intravenous acetaminophen: acelio(R)) leads to enhanced recovery after esophagectomy: a propensity score-matched analysis. *Surg Today*. 2017. https://doi.org/10.1007/s00595-017-1616-5.
16. Sun L, Zhu X, Zou J, Li Y, Han W. Comparison of intravenous and oral acetaminophen for pain control after total knee and hip arthroplasty: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2018;97(6):e9751. https://doi.org/10.1097/MD.0000000000009751.
17. Chidambaran V, Subramanyam R, Ding L, et al. Cost-effectiveness of intravenous acetaminophen and ketorolac in adolescents undergoing idiopathic scoliosis surgery. *Paediatr Anaesth*. 2018. https://doi.org/10.1111/pan.13329.
18. Hansen RN, Pham AT, Boing EA, et al. Hospitalization costs and resource allocation in cholecystectomy with use of intravenous versus oral acetaminophen. *Curr Med Res Opin*. 2018:1–7. https://doi.org/10.1080/03007995.2017.1412301.
19. Sola R Jr, Desai AA, Gonzalez KW, et al. Does intravenous acetaminophen improve postoperative pain control after laparoscopic appendectomy for perforated appendicitis? A prospective randomized trial. *Eur J Pediatr Surg*. 2018. https://doi.org/10.1055/s-0037-1615276.
20. Towers CV, Shelton S, van Nes J, et al. Preoperative cesarean delivery intravenous acetaminophen treatment for postoperative pain control: a randomized double-blinded placebo control trial. *Am J Obstet Gynecol*. 2017. https://doi.org/S0002-9378(17)32692-32693 [pii].
21. Huang PS, Gleason SM, Shah JA, Buros AF, Hoffman DA. Efficacy of intravenous acetaminophen for postoperative analgesia in primary total knee arthroplasty. *J Arthroplasty*. 2017. https://doi.org/S0883-5403(17)30966-X [pii].
22. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH. Prenatal paracetamol exposure and child neurodevelopment: a review. *Horm Behav*. 2018. https://doi.org/S0018-506X(17)30454-3 [pii].
23. Mao J, Chen LL. Gabapentin in pain management. *Anesth Analg*. 2000;91:680–683.
24. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280:1831–1836.
25. Rauck RL, Irving GA, Wallace MS. Once-daily gastroretentive gabapentin for postherpetic neuralgia: integrated efficacy, time to onset of pain relief and safety analyses of data from two phase 3 multicenter, randomized, double-blind, placebo-controlled studies. *J Pain Symptom Manage*. 2013;46:219–228.
26. Beal B, Moeller-Bertram T, Schilling JM. Gabapentin for once-daily treatment of post-herpetic neuralgia: a review. *Clin Interv Aging*. 2012;7:249–255.
27. Collins SL, Moore RA, McQuay HJ. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. *J Pain Symptom Manage*. 2000;20:449–458.
28. Lesser H, Sharma U, LaMoreaux L. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. *Neurology*. 2004;63:2104–2110.
29. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes Care*. 2012;35:2451–2458.
30. Jensen MP, Gammaitoni AR, Bolognese JA, et al. The pain quality response profile of pregabalin in the treatment of neuropathic pain. *Clin J Pain*. 2012;28:683–686.
31. Bialer M. Chemical properties of antiepileptic drugs (AEDs). *Adv Drug Deliv Rev*. 2012;64:887–895.
32. Kothare SV, Kaleyias J. Zonisamide: review of pharmacology, clinical efficacy, tolerability, and safety. *Expert Opin Drug Metab Toxicol*. 2008;4:493–506.
33. Wermeling DP. Ziconotide, an intrathecally administered N-type calcium channel antagonist for the treatment of chronic pain. *Pharmacotherapy*. 2005;25:1084–1094.
34. Backonja MM. Neuropathic pain therapy. From bench to bedside. *Semin Neurol*. 2012;32:264–268.
35. Michiels WB, McGlthlen GL, Platt BJ, Grigsby EJ. Trigeminal neuralgia relief with intrathecal ziconotide. *Clin J Pain*. 2011;7:352–354.
36. Rauck RL, Wallace MS, Burton AW. Intrathecal ziconotide for neuropathic pain: a review. *Pain Pract*. 2009;9:327–337.
37. Lukyanetz EA, Shkryl VM, Kostyuk PG. Selective blockade of N-type calcium channels by levetiracetam. *Epilepsia*. 2002;43:9–18.
38. Crepeau AZ, Treiman DM. Levetiracetam: a comprehensive review. *Expert Rev Neurother*. 2010;10:159–171.
39. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. *Pain*. 2000;87:7–17.
40. Nikolajsen L, Black JA, Kroner K. Neuroma removal for neuropathic pain: efficacy and predictive value of lidocaine infusion. *Clin J Pain*. 2010;26:788–793.
41. Carroll I, Gaeta R, Mackey S. Multivariate analysis of chronic pain patients undergoing lidocaine infusions: increasing pain severity and advancing age predict likelihood of clinically meaningful analgesia. *Clin J Pain*. 2007;23:702–706.

42. Petersen P, Kastrup J, Zeeberg I. Chronic pain treatment with intravenous lidocaine. *Neurol Res*. 1986;8:189–190.
43. Argoff CE, Galer BS, Jensen MP. Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the neuropathic pain scale. *Curr Med Res Opin*. 2004;20(suppl 2):S21–S28.
44. Jungehulsing GJ, Israel H, Safar N, et al. Levetiracetam in patients with central neuropathic post-stroke pain: a randomized, double-blind, placebo-controlled trial. *Eur J Neurol*. 2013;20:331–337.
45. Holbech JV, Otto M, Bach FW. The anticonvulsant levetiracetam for the treatment of pain in polyneuropathy: a randomized, placebo-controlled, cross-over trial. *Eur J Pain*. 2011;15:608–614.
46. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med*. 2009;122(suppl 10):S22–S32.
47. Cruccu G, Truini A. Refractory trigeminal neuralgia: non-surgical treatment options. *CNS Drugs*. 2013;27:91–96.
48. Wang QP, Bai M. Topiramate versus carbamazepine for the treatment of classical trigeminal neuralgia: a meta-analysis. *CNS Drugs*. 2011;5:847–857.
49. Wiffen PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. *Cochrane Database Syst Rev*. 2011;16(2):CD006044.
50. Hershey LA, Bednarczyk EM. Treatment of headache in the elderly. *Curr Treat Options Neurol*. 2013;15:56–62.