Multimodal Analgesia

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Outline

Background of Perioperative Pain

Pathophysiology of pain

Types of Analgesics

Strategies for Perioperative Pain Control

Multimodal Postoperative Pain Control After Orthopaedic Surgery

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Excerpt

Multimodal Analgesia (MMA), also referred to as "balanced analgesia," uses multiple analgesic medications, physical modalities, and cognitive strategies to affect peripheral and central nerve loci for the treatment of pain. In light of the adverse side effects of opioid medication, the MMA model of pain management allows physicians an array of medicine and other modalities to help decrease the morbidity associated with opioid analgesics often used as monotherapy. The number of drug overdoses continues to rise every year, with opioids accounting for nearly two-thirds of the cases and being the leading cause of accidental death in the United States. Orthopedic surgeons are attributed to writing 7.7% of all opioid prescriptions while only accounting for 2.5% of all prescribing physicians.

Orthopedic surgeons are challenged with the task of pain management while mitigating the risk associated with opioids. MMA allows orthopedic surgeons and other medical professionals a more modern and evidence-based approach in treating acute pain in their patients. The use of NSAIDs, acetaminophen, gabapentinoids, immediate-release opioids, cognitive therapy, peri-articular injections, and physical modalities, such as cryotherapy, will be reviewed in this article to assist the modern orthopedic surgeon in controlling pain in their patients in the postoperative period. In addition, this article will review the various drug classes, adverse effects, and contraindications and provide insight into special consideration to certain patients who are opioid-tolerant or suffer from comorbid conditions.

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PMID: 30139215

Designing the ideal perioperative pain management plan starts with multimodal analgesia

Eric S. Schwenk[1] and Edward R. Mariano[2,3]

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Abstract

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Multimodal analgesia is defined as the use of more than one pharmacological class of analgesic medication targeting different receptors along the pain pathway with the goal of improving analgesia while reducing individual class-related side effects. Evidence today supports the routine use of multimodal analgesia in the perioperative period to eliminate the over-reliance on opioids for pain control and to reduce opioid-related adverse events. A multimodal analgesic protocol should be surgery-specific, functioning more like a checklist than a recipe, with options to tailor to the individual patient. Elements of this protocol may include opioids, non-opioid systemic analgesics like acetaminophen, non-steroidal anti-inflammatory drugs, gabapentinoids, ketamine, and local anesthetics administered by infiltration, regional block, or the intravenous route. While implementation of multimodal analgesic protocols perioperatively is recommended as an intervention to decrease the prevalence of long-term opioid use following surgery, the concurrent crisis of drug shortages presents an additional challenge. Anesthesiologists and acute pain medicine specialists will need to advocate locally and nationally to ensure a steady supply of analgesic medications and in-class alternatives for their patients' perioperative pain management.

Keywords: Acute pain management, Ketamine, Multimodal analgesia, Non-opioid analgesics, Opioid epidemic, Regional anesthesia

Review › Clin Podiatr Med Surg. 2019 Oct;36(4):695-705. doi: 10.1016/j.cpm.2019.
Epub 2019 Jul 27.

Opioid Crisis and Acute Pain Management After Foot and Ankle Surgery

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Affiliations + expand

PMID: 31466576 DOI: 10.1016/j.cpm.2019.06.009

Abstract

Opioid abuse has plagued the United States, with a resurgence since the early 2000s. Governmental agencies, pharmaceutical companies, patients, and physicians have all contributed to this crisis. Severe pain has been reported following foot and ankle surgery. There are current national guidelines for chronic opioid prescribing, but guidelines for acute pain have not been established. Prescribing fewer opioids, education on opioid risks, proper disposal of unused medication, and participating in prescription monitoring programs help reduce opioid abuse. Multimodal analgesia is paramount in managing pain while reducing opioid consumption after postoperative foot and ankle surgery.

Keywords: Ankle; Foot; Multimodal; Opioids; Pain; Surgery.

The Numbers

80% of patients experience acute post-op pain

75% rate it as moderate – extreme

Less than 50% report satisfaction with pain control

Poor acute pain control post-op has been linked to persistent/chronic pain (Lancet 2006)

Goals

Perioperative pain control while maintaining motor function

- Physical Therapy
- Occupational Therapy

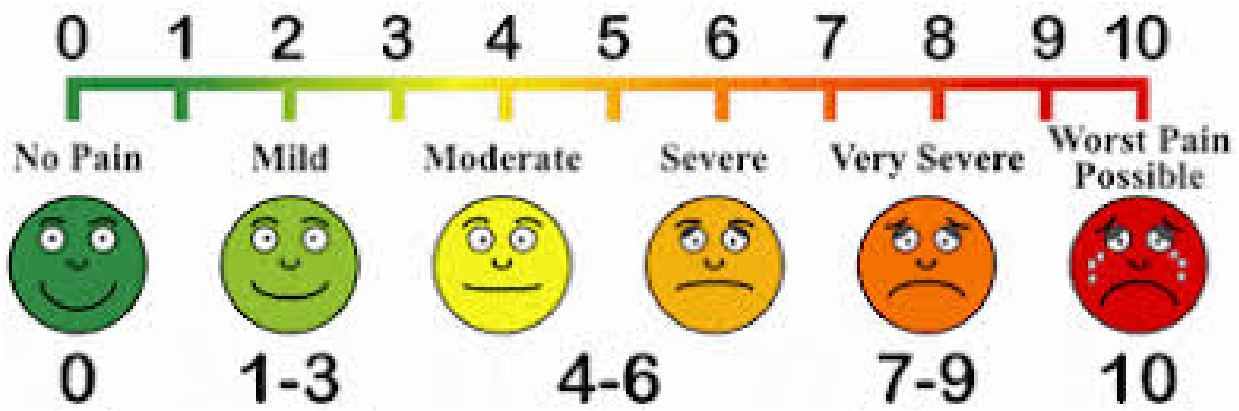
Decrease Opioid Consumption

- Return of Bowel Function
- Cognitive fog, sedation
- We have an opioid problem

Pathophysiology of Pain

Acute
- In response to tissue injury
- A-delta and C sensory fibers (nociceptors)

Chronic
- Persistent activation of these fibers
- Ongoing damage or dysfunction of PNS or CNS > neuropathic pain



Nociceptive
- Pain caused by tissue injury
- Somatic (skin, subcutaneous tissue, fascia, periosteum, joint capsules, etc). Normally sharp or dull localized pain or burning
- Visceral (viscera and surrounding connective tissues). Poorly localized, deep, sometimes cramping; occasionally localized due to nature of injury (organ capsule, etc)

Psychologic factors
- Chronic pain oftentimes associated with psychological distress, depression, anxiety
- Many pain syndromes are multifactorial; (ie, nociceptive + neuropathic)

American Pain Society (APS)

The Journal of Pain
Volume 17, Issue 2, February 2016, Pages 131-157

Guidelines on the Management of Postoperative Pain

Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council

Roger Chou [*], Debra B. Gordon [†], Oscar A. de Leon-Casasola [‡], Jack M. Rosenberg [§], Stephen Bickler [¶], Tim Brennan [‖], Todd Carter [**], Carla L. Cassidy [††], Eva Hall Chittenden [‡‡], Ernest Degenhardt [§§], Scott Griffith [¶¶], Renee Manworren [‖‖], Bill McCarberg [***], Robert Montgomery [†††], Jamie Murphy [‡‡‡], Melissa F. Perkal [§§§], Santhanam Suresh [¶¶¶], Kathleen Sluka [‖‖‖], Scott Strassels [****], Richard Thirlby [††††]...Christopher L. Wu [‡‡‡]

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Treatment of pain

Non opioid analgesics – Acetaminophen, NSAIDs

Antidepressants – TCAs, SNRIs

Gabapentinoids – Gabapentin, Pregabalin

Muscle Relaxants

Opioid analgesics

Glucocorticoids (intraoperative)

NMDA receptor antagonist (intraoperative)

Alpha 2 agonists (intraoperative)

Neuraxial – opioid pumps, spinal cord stimulators

Nerve blocks

Cognitive behavioral therapy

Integrative medicine techniques – acupuncture, relaxation techniques, biofeedback, etc.

APS Recs: Use multimodal analgesia

Nonopioid analgesics: Acetaminophen and NSAIDs

Effective for mild to moderate pain. Act synergistically along with opioids

Acetaminophen: Not anti-inflammatory or antiplatelet; no gastric irritation

- Caution in patients with liver dysfunction
- Maximum of 4g/day, or 1,000 mg QID

NSAIDs: analgesic, anti-inflammatory, antiplatelet

- Inhibit COX enzymes and; therefore, prostaglandin production
  - Non-selective COX inhibitors – ibuprofen, naproxen
  - Semiselective – meloxicam (Mobic)
  - Selective COX-2 inhibitors- celecoxib – lower risk of ulcer formation and GI upset
  - All are prothrombotic – MI, stroke claudication risk
  - Caution in patients with renal dysfunction
  - Topical NSAIDs – diclofenac; patch or gel

Review > Neuropharmacology. 2019 Nov 1;158:107619. doi: 10.1016/j.neuropharm.2019.04.025. Epub 2019 Apr 25.

Combining opioids and non-opioids for pain management: Current status

Jun-Xu Li [1]

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PMID: 31029588 DOI: 10.1016/j.neuropharm.2019.04.025

Abstract

Pain remains a global health challenge. For decades, clinicians have been primarily relying on μ-opioid receptor (MOR) agonists and nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management. MOR agonists remain the most efficacious analgesics available; however, adverse effects related to MOR agonists use are severe which often lead to forced drug discontinuation and inadequate pain relief. The recent opioid overdose epidemic urges the development of safer analgesics. Combination therapy is a well-established clinical pharmacotherapeutic strategy for the treatment of various clinical disorders. The combination of MOR agonists with non-MOR agonists may increase the analgesic potency of MOR agonists, reduce the development of tolerance and dependence, reduce the diversion and abuse, overdose, and reduce other clinically significant side effects associated with prolonged opioid use such as constipation. Overall, the combination therapy approach could substantially improve the therapeutic profile of MOR agonists. This review summarizes some recent developments in this field. This article is part of the Special Issue entitled 'New Vistas in Opioid Pharmacology'.

Keywords: Abuse liability; Antagonists; Combination therapy; Opioids; Pain; Tolerance.

APS Recs: Use multimodal analgesia

Nonopioid Analgesics

Class	Drug	Usual Dosage Range*
Indoles	Diclofenac	50–100 mg, followed by 50 mg every 8 hours 75 mg every 12 hours IV or IM
	Etodolac	200–400 mg every 6–8 hours
	Indomethacin	25–50 mg every 6–8 hours
	Sulindac	150–200 mg every 12 hours
	Tolmetin	200–400 mg every 6–8 hours
Naphthylalkanone	Nabumetone	1000–2000 mg every 24 hours
Oxicam	Piroxicam	20–40 mg every 24 hours
Para-aminophenol derivative	Acetaminophen	650–1000 mg every 6–8 hours
Propionic acids	Fenoprofen	200–600 mg every 6 hours
	Flurbiprofen	50–200 mg every 12 hours
	Ibuprofen†	400 mg every 4 hours to 800 mg every 8 hours (maximum: 3200 mg/day†)
	Ketoprofen	25–50 mg every 6–8 hours
	Naproxen	250–500 mg every 12 hours
	Naproxen sodium	275–550 mg every 12 hours
	Oxaprozin	600–1200 mg every 24 hours
Salicylates	Aspirin	650–1000 mg every 4–6 hours
	Choline magnesium trisalicylate	870 mg every 12 hours
	Diflunisal	250–500 mg every 8–12 hours
	Salsalate	750–2000 mg every 12 hours
Fenamates	Meclofenamate	50–100 mg every 6–8 hours
	Mefenamic acid	250 mg every 6 hours
Pyrazole	Phenylbutazone	100 mg every 6–8 hours up to 7 days
Pyrrolo-pyrrolo derivative	Ketorolac	15–30 mg IV or IM every 6 hours or 20 mg orally, followed by 10 mg orally every 4–6 hours for maximum 5 days (assess creatinine every 4–6 doses, particularly in patients who are older or at risk of renal failure [eg, postoperative patients])
Selective COX-2 inhibitor	Celecoxib	100–200 mg every 12 hours

* Route is oral, except for ibuprofen, ketorolac, diclofenac, and acetaminophen, which can be given parenterally as well as orally. There is a topical form of diclofenac.

† For ibuprofen, dosages ≤ 2400 mg reduce cardiovascular risk and are recommended for patients with cardiovascular risk factors.

COX = cyclooxygenase.

Muscle Relaxants

Tizanidine (Zanaflex): alpha-2 agonist – CNS and anxiolysis; drowsiness, hypotension, QT prolongation

Cyclobenzaprine (Flexeril): 5-HT2 receptor antagonist; dizziness, tachycardia

Methocarbamol (Robaxin): RAS?; least sedating muscle relaxant; IV formulation should not be used in patient's with renal dysfunction (polyethelene glycol > worsening of acidosis)

Baclofen: GABA analog; spasticity; withdrawal common upon cessation

Diazepam (Valium): positive allosteric modulators of the GABA type A receptors; anxiolytic; sedation

Caution in elderly

Muscle spasms common after orthopedic surgery; "cramping, pulling, tight"

Opioid analgesics

Proven efficacy for acute pain, cancer-related pain, and as part of palliative care

Generally, short-acting (immediate release) agonists are used for acute pain at the lowest effective dose

- CDC recommends 3-7 days; patient's should be reevaluated before re-prescribing opioids
- Long-duration and high dose opioid use increases risk of adverse effects and opioid misuse
- Patient's should be transitioned off of opioids (and continued on multimodals) ASAP after trauma/surgery

Adverse effects

- opioid use disorder, overdose, respiratory depression, somnolence, nausea/vomiting, constipation

Opioid analgesics

Physical dependence should be assumed in all patients on opioids for more than a few days

- Withdrawal symptoms; taper off; use as little as possible
- Physical dependence is not the same as opioid use disorder, which involves compulsive use, loss of control, craving, etc.

Tolerance develops in all patients treated with opioids

- Decreased response to same dose of a drug when used repeatedly

Can consider opioid agonists-antagonists, especially in patients with OUD or history of addiction instead of pure opioid agonists (buprenorphine)

- Patient will receive analgesic benefit without the “high” associated with pure opioid agonists
- Have a ceiling effect for analgesia; be aware that they will precipitate withdrawal in a patient already physically dependent on opioids

Opioid analgesics: Dosing and titration

Opioid naïve patient

- start at the lowest available starting dose of IR formulation and increase incrementally as tolerated by patient until adequate analgesic or dose-limiting side effects
- Combination drugs (Norco, Percocet) – opioid dose may become limited by acetaminophen dose
- Older patients more sensitive
- Do not start with a long-acting narcotic (oxycontin) in an opioid naïve patient; prone to adverse effects
- Can consider PCA if patient unable to take medications orally

Opioid tolerant patient

- Will require ~ 2x amount of narcotic on at baseline (anecdotal)

Caution in patients with hepatic disorders, COPD, OSA, dementia (delirium), renal insufficiency (fentanyl and methadone metabolites)

- Caution in co-administering with benzodiazepines
- Always have naloxone available

APS Recs: Use PO instead of IV

Initial PO opioid dosing ranges (naiive)

Common dosage range: Oxycodone 2.5-15 mg PO q4h PRN	
Elderly or high-risk	2.5-5 mg PO q4h PRN (starting dose)
Young, low-risk	5-10 mg PO q4h PRN (starting dose)

Common dosage range: Hydromorphone 1-6 mg PO q4h PRN	
Elderly or high-risk	1-2 mg PO q4h PRN (starting dose)
Young, low-risk	2-4 mg PO q4h PRN (starting dose)

APS Recs: Use PO instead of IV

Initial breakthrough IV dosage

Common dosage range: Hydromorhone 0.2-1 mg PO q4h PRN	
Elderly or high-risk	0.2 mg IV q2h PRN (starting dose)
Young, low-risk	0.4 mg IV q2h PRN (starting dose)

Common dosage range: Morphine 1-5 mg PO q4h PRN	
Elderly or high-risk	1 mg IV q2h PRN (starting dose)
Young, low-risk	2 mg IV q2h PRN (starting dose)

APS Recs: Use PO instead of IV

Opioid Analgesics

Drug	Adult Dose*	Pediatric Dose†	Comments
Opioid agonists in combination products‡ for moderate pain			
Codeine	**Oral:** 30–60 mg every 4–6 hours as needed	—	Less potent than morphine
Hydrocodone	**Oral:** 5–10 mg every 4–6 hours as needed	—	More potent than codeine
Opioid agonists for moderate-to-severe pain			
Fentanyl	**Transdermal:** 12 or 25 mcg/hour every 3 days **Transmucosal:** 100–200 mcg every 2–4 hours **Intranasal:** 100–200 mcg every 2–4 hours **Parenteral:** 25–100 mcg every 30–60 minutes IV or as patient-controlled analgesia	**Parenteral:** 1–2 mcg/kg/dose IV; may be repeated in 2–4 hours as needed	May trigger less histamine release and thus may cause less hypotension than other opioids **Transdermal:** When used in cachectic patients, may result in erratic absorption and blood levels Supplemental analgesia required at first because peak analgesia does not occur until 18–24 hours after application May take many hours for adverse effects to resolve after removing patch **Short-acting transmucosal and intranasal forms:** Used for breakthrough pain in opioid-tolerant adults

Drug	Adult Dose*	Pediatric Dose†	Comments
			and for conscious sedation in children **IV form:** Sometimes used for procedural sedation
Hydromorphone	**Oral immediate release:** 2–4 mg every 4–6 hours **Oral extended-release:** 8–32 mg every 24 hours **Oral liquid:** 2.5–10 mg every 4–6 hours **Parenteral:** 0.2–1 mg every 4–6 hours or as patient-controlled analgesia **Rectal:** 3 mg every 6–8 hours	—	Short half-life **Rectal form:** Used at bedtime
Methadone	**Oral:** 2.5–10 mg every 8–12 hours **Parenteral:** 2.5–10 mg IM or IV every 8–12 hours	—	Used for treatment of heroin withdrawal, long-term maintenance treatment of opioid use disorder, and analgesia for chronic pain Establishment of a safe, effective dose for analgesia complicated by its long half-life (usually much longer than duration of analgesia) Requires close monitoring for several days or more after amount or frequency of dose is increased because serious toxicity can occur as the plasma level rises to steady state

Drug	Adult Dose*	Pediatric Dose†	Comments
			Risk of QT-interval prolongation; ECG monitoring recommended
Morphine	**Oral immediate-release:** 5–30 mg every 4 hours **Oral controlled-release:** 15 mg every 12 hours **Oral sustained-release:** 30 mg every 24 hours **Parenteral:** 2–5 mg IV or IM every 2–4 hours as needed	> 6 months old and < 50 kg: • **Oral immediate-release tablet or oral solution:** 0.2–0.5 mg/kg/dose every 3–4 hours as needed (usual initial maximum dose 15–20 mg/dose) • **IV (preferred), subcutaneous, IM (IM not recommended):** 0.05 mg/kg/dose every 2–4 hours as needed (initial maximum dose 1–2 mg/dose) > 6 months old and ≥ 50 kg: • **Oral immediate-release tablets or oral solution:** 15–20 mg every 3–4 hours as needed. • **Parenteral (IV, subcutaneous, or IM):** 2–5 mg/dose every 2–4 hours as needed	Standard of comparison Triggers histamine release more often than other opioids, causing itching

Drug	Adult Dose*	Pediatric Dose†	Comments
Oxycodone‡	**Oral:** 5–10 mg every 6 hours **Oral controlled-release:** 10–20 mg every 12 hours	—	Also in combination products containing acetaminophen or aspirin
Opioid agonist-antagonists§			
Buprenorphine	**IV or IM:** 0.3 mg every 6 hours **Sublingual:** 75 mcg once a day or, if tolerated, every 12 hours for ≥ 4 days, then increased to 150 mcg every 12 hours **Transdermal patch:** initially 5mcg/hour applied once a week; may be titrated to 20 mcg/hour once a week	Use only in patients > 13 years (same as adult dose)	Psychotomimetic effects (eg, delirium, sedation) less prominent than those of other agonist-antagonists, but other effects similar Lower risk of respiratory depression with buprenorphine than with traditional analgesics (eg, morphine, fentanyl) but not fully reversible with naloxone Higher affinity for mu receptors than traditional analgesics

Drug	Adult Dose*	Pediatric Dose†	Comments
			May induce acute withdrawal if added to long-term opioid therapy Analgesic effect of traditional analgesics possibly limited when they are added to long-term therapy with buprenorphine Sublingual and transdermal buprenorphine used occasionally for chronic pain May be used as agonist therapy in opioid use disorder but requires special licensure
Tramadol	**Oral immediate-release:** 50–100 mg every 4–6 hours; maximum 400 mg/day **Oral extended-release:** 100 mg once a day; increase by ≤ 100 mg/day every 5 days to a dose of ≤ 300 mg total daily dose	Not recommended	Less potential for abuse than with other opioids Not as potent as other opioid analgesics

* Starting doses are for opioid-naive patients. Patients with opioid tolerance or severe pain may require higher doses.

† Not all drugs are appropriate for analgesia in children.

‡ These opioid agonists may be combined into a single pill with acetaminophen, aspirin, or ibuprofen. They are often used alone so that acetaminophen, aspirin, or ibuprofen dosing limits do not limit opioid dosing. If combination therapy is desired, acetaminophen, aspirin, or ibuprofen can be added separately while maximizing flexibility in dosing the opioid agonist.

§ Opioid agonist-antagonists are not usually used for chronic pain and are rarely drugs of choice for older patients.

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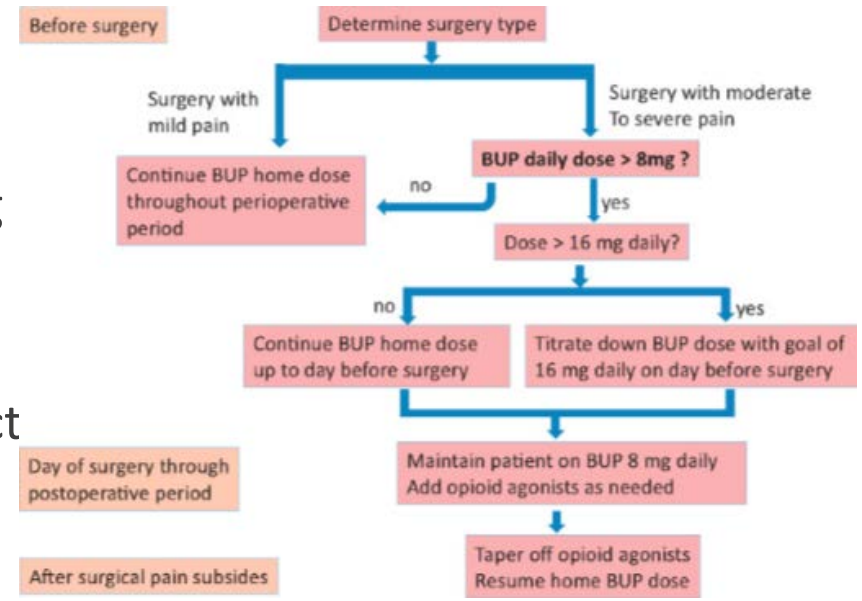
Buprenorphine

Chronic pain

- Likely high opioid tolerance and hypersensitivity to pain
- Transdermal, buccal
- Can consider adding direct-acting agonists

MAT

- High risk of relapse with direct-act opioid agonists
- Sublingual, IM depot, subdermal
- Continue home dose and add
- Doses >24 mg/day, no benefit



Review > Reg Anesth Pain Med. 2021 Oct;46(10):840-859. doi: 10.1136/rapm-2021-103007. Epub 2021 Aug 12.

Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel

Lynn Kohan [1], Sudheer Potru [2 3], Antje M Barreveld [4], Michael Sprintz [5], Olabisi Lane [6], Anuj Aryal [7], Trent Emerick [8], Anna Dopp [9], Sophia Chhay [9], Eugene Viscusi [10]

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PMID: 34385292 DOI: 10.1136/rapm-2021-103007

Abstract

Background: The past two decades have witnessed an epidemic of opioid use disorder (OUD) in the USA, resulting in catastrophic loss of life secondary to opioid overdoses. Medication treatment of opioid use disorder (MOUD) is effective, yet barriers to care continue to result in a large proportion of untreated individuals. Optimal analgesia can be obtained in patients with MOUD within the perioperative period. Anesthesiologists and pain physicians can recommend and consider initiating MOUD in patients with suspected OUD at the point of care; this can serve as a bridge to comprehensive treatment and ultimately save lives.

Methods: The Board of Directors of the American Society of Regional Anesthesia and Pain Medicine, American Society of Anesthesiologists, American Academy of Pain Medicine, American Society of Addiction Medicine and American Society of Health System Pharmacists approved the creation of a Multisociety Working Group on Opioid Use Disorder, representing the fields of pain medicine, addiction, and pharmacy health sciences. An extensive literature search was performed by members of the working group. Multiple study types were included and reviewed for quality. A modified Delphi process was used to assess the literature and expert opinion for each topic, with 100% consensus being achieved on the statements and each recommendation. The consensus statements were then graded by the committee members using the United States Preventive Services Task Force grading of evidence guidelines. In addition to the consensus recommendations, a narrative overview of buprenorphine, including pharmacology and legal statutes, was performed.

Results: Two core topics were identified for the development of recommendations with >75% consensus as the goal for consensus; however, the working group achieved 100% consensus on both topics. Specific topics included (1) providing recommendations to aid physicians in the management of patients receiving buprenorphine for MOUD in the perioperative setting and (2) providing recommendations to aid physicians in the initiation of buprenorphine in patients with suspected OUD in the perioperative setting.

Conclusions: To decrease the risk of OUD recurrence, buprenorphine should not be routinely discontinued in the perioperative setting. Buprenorphine can be initiated in untreated patients with OUD and acute pain in the perioperative setting to decrease the risk of opioid recurrence and death from overdose.

Keywords: analgesics; opioid; opioid-related disorders; pain; pain management; pharmacology; postoperative.

Adjuvant medications – Gabapentinoids, TCAs, SNRIs

Can relieve pain, specifically pain with a neuropathic component

TCAs: amitriptyline, nortriptyline

- Blocks reuptake of serotonin and NE

SNRIs : duloxetine

- Serotonin and NE reuptake inhibitor

Gabapentinoids Gabapentin, Pregabalin (Lyrica)

- side effects may outweigh benefits; exceptions for patients on chronic gabapentinoid therapy

Review > Neuroscience. 2016 Dec 3;338:183-206. doi: 10.1016/j.neuroscience.2016.06.057. Epub 2016 Jul 9.

Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights

Mélanie Kremer [1], Eric Salvat [2], André Muller [2], Ipek Yalcin [3], Michel Barrot [4]

Affiliations + expand

PMID: 27401055 DOI: 10.1016/j.neuroscience.2016.06.057

Abstract

Neuropathic pain arises as a consequence of a lesion or disease affecting the somatosensory system. It is generally chronic and challenging to treat. The recommended pharmacotherapy for neuropathic pain includes the use of some antidepressants, such as tricyclic antidepressants (TCAs) (amitriptyline...) or serotonin and noradrenaline re-uptake inhibitors (duloxetine...), and/or anticonvulsants such as the gabapentinoids gabapentin or pregabalin. Antidepressant drugs are not acute analgesics but require a chronic treatment to relieve neuropathic pain, which suggests the recruitment of secondary downstream mechanisms as well as long-term molecular and neuronal plasticity. Noradrenaline is a major actor for the action of antidepressant drugs in a neuropathic pain context. Mechanistic hypotheses have implied the recruitment of noradrenergic descending pathways as well as the peripheral recruitment of noradrenaline from sympathetic fibers sprouting into dorsal root ganglia; and importance of both α2 and β2 adrenoceptors have been reported. These monoamine re-uptake inhibitors may also indirectly act as anti-proinflammatory cytokine drugs; and their therapeutic action requires the opioid system, particularly the mu (MOP) and/or delta (DOP) opioid receptors. Gabapentinoids, which target the voltage-dependent calcium channels α2δ-1 subunit, inhibit calcium currents, thus decreasing the excitatory transmitter release and spinal sensitization. Gabapentinoids also activate the descending noradrenergic pain inhibitory system coupled to spinal α2 adrenoceptors. Gabapentinoid treatment may also indirectly impact on neuroimmune actors, like proinflammatory cytokines. These drugs are effective against neuropathic pain both with acute administration at high dose and with repeated administration. This review focuses on mechanistic knowledge concerning chronic antidepressant treatment and gabapentinoid treatment in a neuropathic pain context.

Keywords: antidepressants; gabapentinoids; monoaminergic system; neuroimmune; neuropathic pain; opioidergic system.

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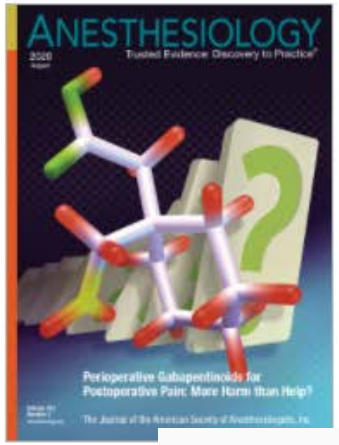

Perioperative Medicine | August 2020

Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain: A Systematic Review and Meta-analysis

FREE

Michael Verret, M.D., M.Sc.; François Lauzier, M.D., M.Sc.; Ryan Zarychanski, M.D., M.Sc.; Caroline Perron, M.Sc.; Xavier Savard, M.D. candidate; Anne-Marie Pinard, M.D., M.Sc.; Guillaume Leblanc, M.D., M.Sc.; Marie-Joëlle Cossi, Ph.D.; Xavier Neveu, M.Sc.; Alexis F. Turgeon, M.D., M.Sc. ... Show more

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Anesthesiology August 2020, Vol. 133, 265–279.

https://doi.org/10.1097/ALN.0000000000003428

Results

In total, 281 trials (N = 24,682 participants) were included in this meta-analysis. Compared with controls, gabapentinoids were associated with a lower postoperative pain intensity (100-point scale) at 6 h (mean difference, −10; 95% CI, −12 to −9), 12 h (mean difference, −9; 95% CI, −10 to −7), 24 h (mean difference, −7; 95% CI, −8 to −6), and 48 h (mean difference, −3; 95% CI, −5 to −1). This effect was not clinically significant ranging below the minimally important difference (10 points out of 100) for each time point. These results were consistent regardless of the type of drug (gabapentin or pregabalin). No effect was observed on pain intensity at 72 h, subacute and chronic pain. The use of gabapentinoids was associated with a lower risk of postoperative nausea and vomiting but with more dizziness and visual disturbance.

Conclusions

No clinically significant analgesic effect for the perioperative use of gabapentinoids was observed. There was also no effect on the prevention of postoperative chronic pain and a greater risk of adverse events. These results do not support the routine use of pregabalin or gabapentin for the management of postoperative pain in adult patients.

Drugs for Neuropathic Pain

Class/Drug	Dose*	Comments
Antiseizure drugs†		
Carbamazepine	200–400 mg twice a day	Monitor CBC and liver function during treatment May decrease efficacy of oral contraceptives First-line treatment for trigeminal neuralgia
Gabapentin	300–1200 mg 3 times a day	Starting dose usually 300 mg once a day Dosing goal: 600–1200 mg 3 times a day Adjust dose in patients with renal insufficiency
Oxcarbazepine	600–1200 mg twice a day	Starting dose usually 300 mg once a day Considered as efficacious as carbamazepine for trigeminal neuralgia and useful for other paroxysmal neuropathic pain May cause hyponatremia or decrease efficacy of oral contraceptives Unlike carbamazepine, no CBC or liver function monitoring necessary
Phenytoin	300 mg once a day	Limited data; 2nd-line drug
Pregabalin	150–300 mg twice a day	Mechanism similar to gabapentin but more stable pharmacokinetics
Antidepressants		
Amitriptyline	10–25 mg at bedtime (starting dose), increased weekly by the same dose to a maximum of 150 mg at bedtime	Dosing goal: About 100 mg/day (dosing for pain unlikely to be adequate for relieving depression or anxiety) Not recommended for older patients or patients with a heart disorder because it has strong anticholinergic effects May increase dose to 150 mg or sometimes higher
Desipramine or nortriptyline	10–25 mg at bedtime (starting dose), increased weekly by the same dose to maximum of 150 mg at bedtime	Better tolerated than amitriptyline; adverse effect profile better with desipramine than nortriptyline Dosing goal: About 100 mg/day (dosing for pain unlikely to be adequate for relieving depression or anxiety) Not recommended for older patients or patients with a heart disorder because it has strong anticholinergic effects
Duloxetine	20–60 mg once a day (starting dose) Starting at 20–30 mg once a day and increasing by the same dosage weekly to a goal of 60 mg/day; in some cases, increasing to 60 mg twice a day (especially in patients with concomitant depression or anxiety)	Better tolerated than tricyclic antidepressants Dosing goal for pain (60 mg/day) usually sufficient to treat concomitant depression or anxiety

* Route is oral unless otherwise indicated.

† Topical lidocaine 4–5% applied 1 hour before applying capsaicin can help limit irritation.

CBC = complete blood count; EMLA = eutectic mixture of local anesthetics; GABA = gamma-aminobutyric acid; NMDA = *N*-methyl-D-aspartate; WBCs = white blood cells.

Nerve blocks

Interrupt nerve transmission in peripheral or central pain pathways

Can be performed before or after procedure

Must determine appropriate type of block, intended length of duration, appropriate drug and dosage, and manage side effects (motor block, LAST)

Consider for high pain-score surgeries

Typical preop regimen:

- Regional technique (if amenable)
- Acetaminophen 1000 mg PO
- Celecoxib 400 mg PO
- Methocarbamol 500 mg PO

Typical postop regimen:

- Regional technique (nerve block)
- Acetaminophen 1000 mg PO q6h
- Celecoxib 200 mg PO BID
- Methocarbamol 500 mg PO QID
- Oxycodone 5-10 mg PO q4h PRN

Take Home

Use Multimodal Analgesia (Acetaminophen, NSAIDS, muscle relaxants, antidepressants)

Have multiple tools in your belt (regional techniques, familiarity with several classes of medications and know their side effects/contraindications)

Use Opioids as a supplement and wean off as soon as is appropriate

Phew! Questions?

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